AN 2001:545691 CAPLUS
DN 135:127219
TI Preparation of pseudopolymorph of Flavopiridol
IN Bafus, Gary L.; Harrison-Bowman, Christine M.; Silvey, Gary L.
PA Aventis Pharmaceuticals Inc., USA
SO PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001053293	A1	20010726	WO 2001-US519	20010108
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	BR 2001007726	A	20021001	BR 2001-7726	20010108
	EP 1259507	A1	20021127	EP 2001-900939	20010108
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2003520797	T2	20030708	JP 2001-553767	20010108
	NO 2002003386	A	20020912	NO 2002-3386	20020712
PRAI	US 2000-484717	A2	20000118		
	WO 2001-US519	W	20010108		

AB Prepn. of a pseudopolymorph of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]- H-1-benzopyran-4-one hydrochloride (Flavopiridol HCl, Form I), essentially free of Form II (an ethanol solvate or hydrate), a pharmaceutical compn. comprising a therapeutically effective Form I and a carrier, and methods of using the pseudopolymorph for inhibiting protein kinases are described. For example, Flavopiridol Form I was prepd. by crystn. from Form II azeotropic mixt. with ketone, i.e., Me Et ketone, and filtration of crystd. Form I.

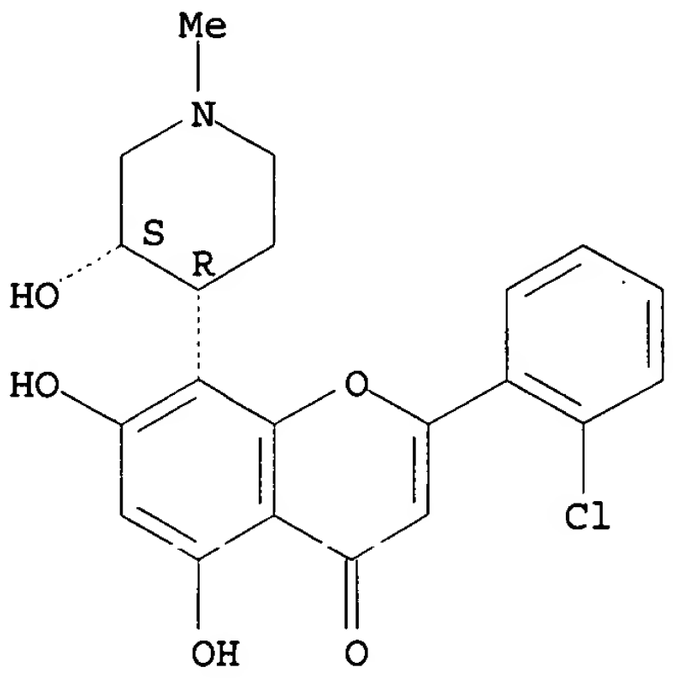
IT **351184-34-4P 351184-35-5P**
RL: PEP (Physical, engineering or chemical process); SPN (Synthetic preparation); PREP (Preparation); PROC (Process)
(prepn. and compns. of pseudopolymorph of Flavopiridol as protein kinase inhibitor)

RN 351184-34-4 CAPLUS
CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-, hydrochloride, compd. with ethanol, hydrate (9CI) (CA INDEX NAME)

CM 1

CRN 131740-09-5
CMF C21 H20 Cl N O5 . Cl H

Absolute stereochemistry. Rotation (-).



● HCl

CM 2

CRN 64-17-5
CMF C2 H6 O

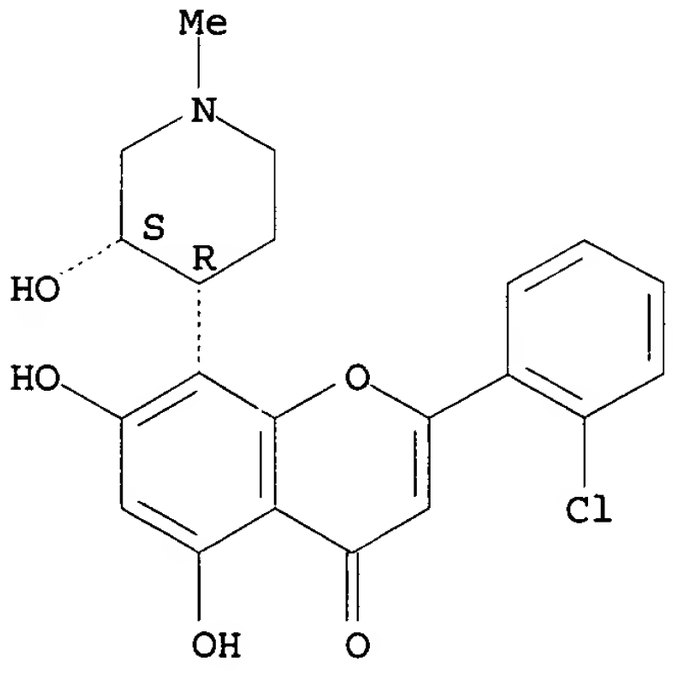
H_3C-CH_2-OH

RN 351184-35-5 CAPLUS
CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-, compd. with 2-butanone (9CI) (CA INDEX NAME)

CM 1

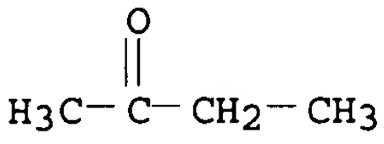
CRN 146426-40-6
CMF C21 H20 Cl N O5

Absolute stereochemistry. Rotation (-).



CM 2

CRN 78-93-3
CMF C4 H8 O



RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AN 2001:545692 CAPLUS
DN 135:127220
TI Preparation of ethanol solvate of Flavopiridol for cancer treatment
IN Kesseler, Kurt M.
PA Aventis Pharmaceuticals Inc., USA
SO PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001053294	A1	20010726	WO 2001-US520	20010108
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	BR 2001007724	A	20021001	BR 2001-7724	20010108
	EP 1252155	A1	20021030	EP 2001-902993	20010108
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2003520798	T2	20030708	JP 2001-553768	20010108
	US 2001051638	A1	20011213	US 2001-760590	20010116
	NO 2002003385	A	20020827	NO 2002-3385	20020712
PRAI	US 2000-487815	A2	20000118		
	US 2000-287593P	P	20000118		
	WO 2001-US520	W	20010108		

AB An ethanol solvate form of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one (Flavopiridol, Form II), a method of making Form II and a compn. comprising Form II are described. The Form II was prepd. using (-)-cis-1-methyl-4R-(2,4,6-trimethoxyphenyl)-3S-piperidinol as the starting compd. Since Flavopiridol is useful in treating a no. of conditions or diseases that benefit from inhibition of protein kinases, and more particularly cyclin-dependent kinases, including cancer, the Form II is useful for prepn. of a pharmaceutical compn. for treating cancer.

IT **351184-37-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn., properties and compns. of ethanol solvate of Flavopiridol for cancer treatment)

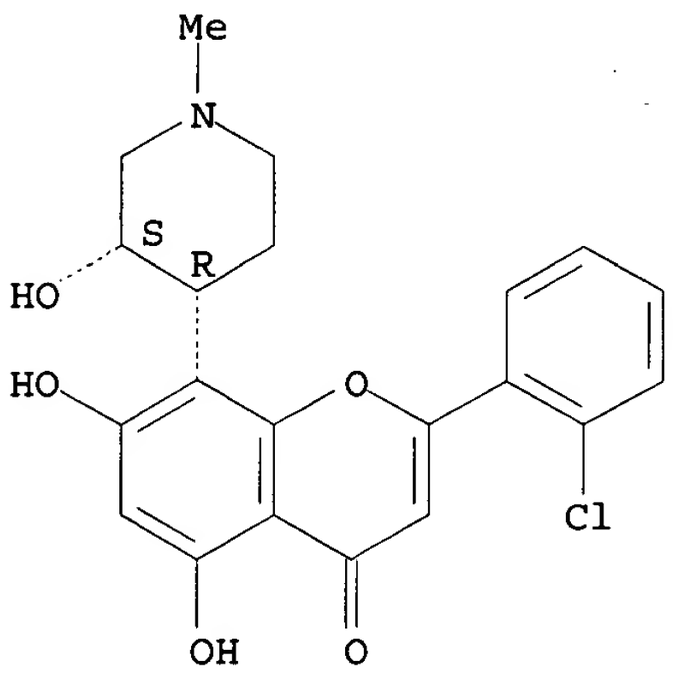
RN 351184-37-7 CAPLUS

RN **351184-37-7** REGISTRY
CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-, hydrochloride, compd. with ethanol (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ethanol, compd. with 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-4H-1-benzopyran-4-one hydrochloride (9CI)
FS STEREOSEARCH
MF C21 H20 Cl N O5 . x C2 H6 O . Cl H
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

CM 1

CRN 131740-09-5 (146426-40-6)
CMF C21 H20 Cl N O5 . Cl H

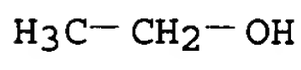
Absolute stereochemistry. Rotation (-).



● HCl

CM 2

CRN 64-17-5
CMF C2 H6 O



1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

AN 2001:434848 CAPLUS
DN 135:51044
TI Pharmaceutical preparation for treating tumor diseases
IN Ghyczy, Miklos; Hager, Joerg; Wendel, Armin
PA Rhone-Poulenc Rorer Gmbh, Germany
SO PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001041747	A2	20010614	WO 2000-EP11761	20001125
	WO 2001041747	A3	20020207		
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	DE 19959546	A1	20010621	DE 1999-19959546	19991209
	EP 1239862	A2	20020918	EP 2000-979624	20001125
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2003516348	T2	20030513	JP 2001-543092	20001125
	US 2001021704	A1	20010913	US 2000-731787	20001208
PRAI	DE 1999-19959546	A	19991209		
	WO 2000-EP11761	W	20001125		

AB The invention relates to a pharmaceutical prepn. contg. at least one active substance that is cytostatically active, at least one biol. electron acceptor, and the customary pharmaceutical additives. The invention also relates to the use of said prepn. for treating tumor diseases, in particular, for treating cancer. Electron acceptors are betaine, phospholipids, their derivs. etc. Thus 100 g **flavopiridol**-HCl, 2000 g phosphatidylcholine, 40 g distearoylphosphatidylglycerol, and 250 g betaine linoleate were dispersed in 10 L **ethanol**; liposomes were formed. The dispersion was added to a soln. of 2 kg maltose in 2 L water, and homogenized. After filtration the dispersion was filled into vials and freeze-dryed to yield 100 mg **flavopiridol** per vial.

2/5/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13932715 BIOSIS NO.: 200200561536
A high-performance liquid chromatography method using ultraviolet detection for the quantitation of flavopiridol from human plasma.
AUTHOR: Zhai Suoping; Sausville Edward; Figg William D(a)
AUTHOR ADDRESS: (a)National Cancer Institute, 9000 Rockville Pike, Building 10, Room 5A01, Bethesda, MD, 20892**USA E-Mail: wdfigg@helix.nih.gov
JOURNAL: Biomedical Chromatography 16 (6):p379-382 September, 2002
MEDIUM: print
ISSN: 0269-3879
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Flavopiridol is an inhibitor of cyclin-dependent kinase, a key regulator of cell cycle, and is currently under clinical trials. We developed and validated an HPLC assay method for the quantitation of **flavopiridol** in human plasma samples. The sample preparation consisted of protein precipitation with **acetonitrile**. Separation was accomplished on a C18 column and a C18 precolumn insert utilizing a gradient profile consisting of ammonium acetate and **methanol**. Ultraviolet detection was set at 268 nm for **flavopiridol** and 323 nm for umbelliferone, the internal standard. The method was validated over flavopiridol concentration range of 0.025-3.0 mug/mL using 250 muL of plasma. The assay was linear over this concentration range with a coefficient of variation less than 10% for inter- and intra-assay. The retention times were around 6.2 min for umbelliferone and 9.8 min for flavopiridol. The recoveries of flavopiridol and umbelliferone were 88.6 +- 1.0% and 97.1 +- 3.7%, respectively. This method is suitable for quantifying flavopiridol in plasma samples and further characterizing the clinical pharmacology of this compound.

REGISTRY NUMBERS: 75-05-8: ACETONITRILE; 631-61-8: AMMONIUM ACETATE; 150428-23-2: CYCLIN-DEPENDENT KINASE; 146426-40-6: FLAVOPIRIDOL; 67-56-1: METHANOL; 93-35-6: UMBELLIFERONE

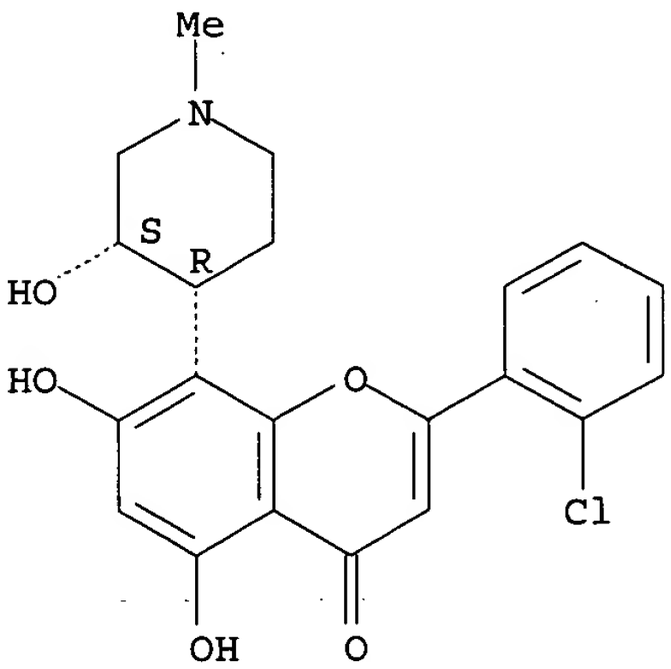
=> d 1-9 sub can

L2 ANSWER 1 OF 10 REGISTRY COPYRIGHT 2002 ACS
RN **351184-35-5** REGISTRY
CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-, compd. with 2-butanone (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2-Butanone, compd. with 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-4H-1-benzopyran-4-one (9CI)
FS STEREOSEARCH
MF C21 H20 Cl N O5 . x C4 H8 O
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

CM 1

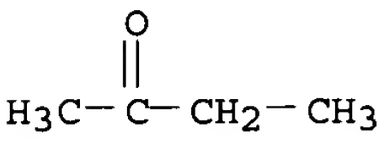
CRN 146426-40-6
CMF C21 H20 Cl N O5

Absolute stereochemistry. Rotation (-).



CM 2

CRN 78-93-3
CMF C4 H8 O



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:127219

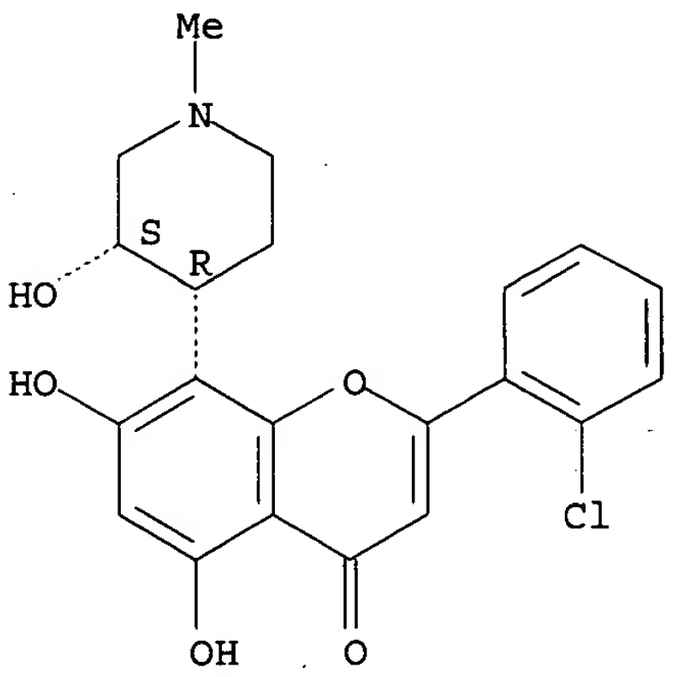
L2 ANSWER 2 OF 10 REGISTRY COPYRIGHT 2002 ACS
RN **351184-34-4** REGISTRY
CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-, hydrochloride, compd. with ethanol, hydrate (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ethanol, compd. with 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-

1-methyl-4-piperidinyl]-4H-1-benzopyran-4-one hydrochloride, hydrate (9CI)
FS STEREOSEARCH
MF C21 H20 Cl N O5 . x C2 H6 O . Cl H . x H2 O
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

CM 1

CRN 131740-09-5 (146426-40-6)
CMF C21 H20 Cl N O5 . Cl H

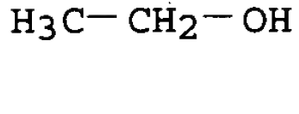
Absolute stereochemistry. Rotation (-).



● HCl

CM 2

CRN 64-17-5
CMF C2 H6 O

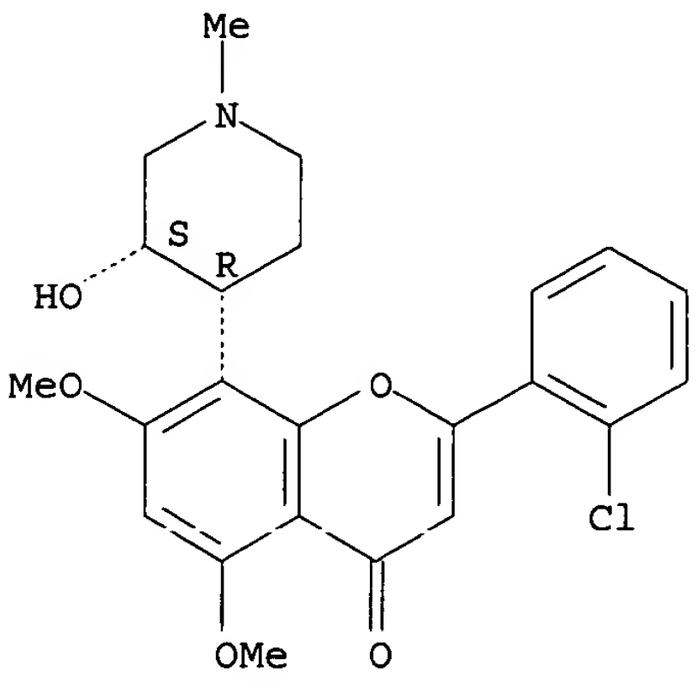


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:127219

L2 ANSWER 3 OF 10 REGISTRY COPYRIGHT 2002 ACS
RN **205506-16-7** REGISTRY
CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-5,7-dimethoxy- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-8-(3-hydroxy-1-methyl-4-piperidinyl)-5,7-dimethoxy-, (3S-cis)-
FS STEREOSEARCH
MF C23 H24 Cl N O5
SR CA
LC STN Files: CA, CAPLUS, CASREACT, TOXCENTER, TOXLIT, USPATFULL

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

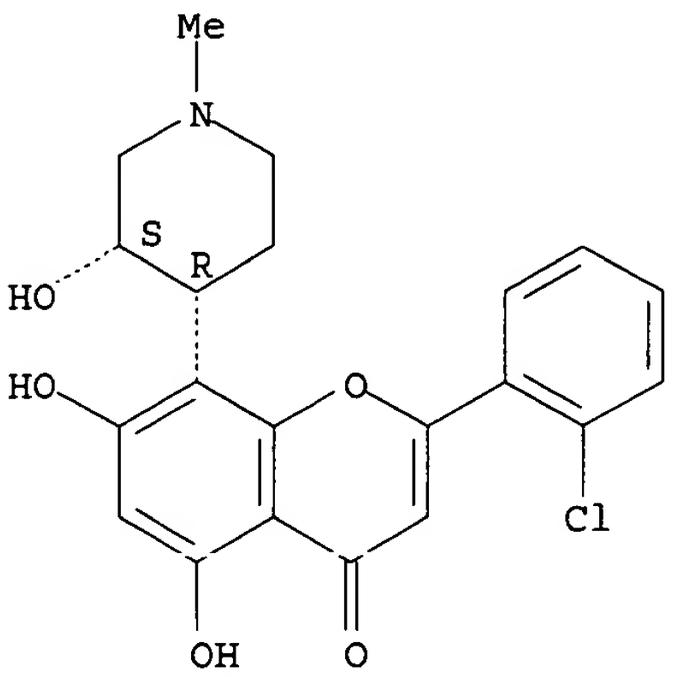
REFERENCE 1: 135:127220

REFERENCE 2: 135:127219

REFERENCE 3: 128:270537

L2 ANSWER 4 OF 10 REGISTRY COPYRIGHT 2002 ACS
RN **146426-40-6** REGISTRY
CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-(3-hydroxy-1-methyl-4-piperidinyl)-, cis-(-)-
OTHER NAMES:
CN Flavopiridol
CN HMR 1275
CN L 86-8275
FS STEREOSEARCH
MF C21 H20 Cl N O5
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, SYNTHLINE, TOXCENTER, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (-).



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114 REFERENCES IN FILE CA (1967 TO DATE)
11 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
115 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 136:68517

REFERENCE 2: 136:48107

REFERENCE 3: 136:31648

REFERENCE 4: 136:31647

REFERENCE 5: 135:362557

REFERENCE 6: 135:338869

REFERENCE 7: 135:298314

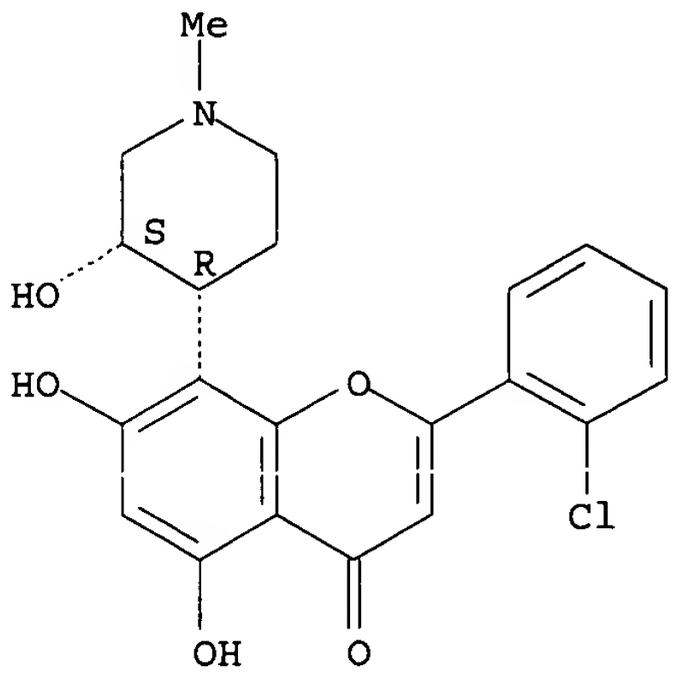
REFERENCE 8: 135:282454

REFERENCE 9: 135:251976

REFERENCE 10: 135:220798

L2 ANSWER 5 OF 10 REGISTRY COPYRIGHT 2002 ACS
RN **131740-09-5** REGISTRY
CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-, hydrochloride (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-(3-hydroxy-1-methyl-4-piperidinyl)-, hydrochloride, cis-(-)-
OTHER NAMES:
CN NSC 649890
FS STEREOSEARCH
MF C21 H20 Cl N O5 . Cl H
CI COM
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, DRUGNL, DRUGUPDATES, MRCK*, SYNTHLINE, TOXCENTER, TOXLIT, USPATFULL
(*File contains numerically searchable property data)
CRN (146426-40-6)

Absolute stereochemistry. Rotation (-).



● HCl

7 REFERENCES IN FILE CA (1967 TO DATE)
7 REFERENCES IN FILE CAPLUS (1967 TO DATE)

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REFERENCE 2: 135:127219

REFERENCE 3: 132:329515

REFERENCE 4: 129:170064

REFERENCE 5: 128:188361

REFERENCE 6: 126:216569

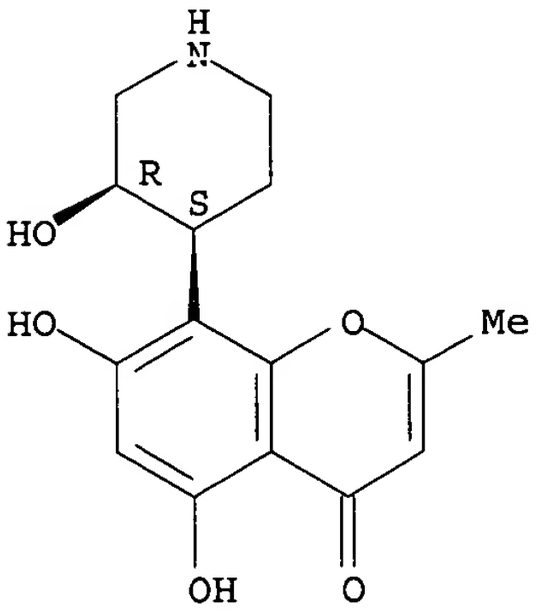
REFERENCE 7: 114:61928

L2 ANSWER 6 OF 10 REGISTRY COPYRIGHT 2002 ACS
RN **113225-21-1** REGISTRY
CN Ethanone, 1-[2-hydroxy-3-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-4,6-dimethoxyphenyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ethanone, 1-[2-hydroxy-3-(3-hydroxy-1-methyl-4-piperidinyl)-4,6-dimethoxyphenyl]-, cis-(-)-
OTHER NAMES:
CN Acetoflocinipiperidol
FS STEREOSEARCH
MF C16 H23 N O5
CI COM
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, TOXCENTER, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (-).

L5 79 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 4H-1-Benzopyran-4-one, 5,7-dihydroxy-8-(3-hydroxy-4-piperidinyl)-2-methyl-, cis-(-)- (9CI)
MF C15 H17 N O5
CI COM

Rotation (-). Absolute stereochemistry unknown.



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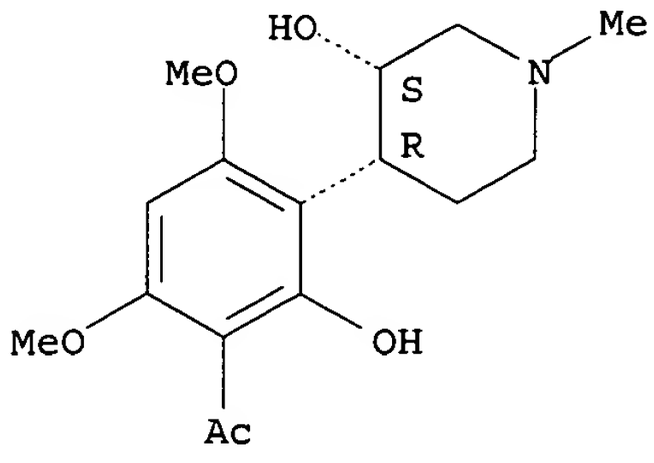


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

7 REFERENCES IN FILE CA (1967 TO DATE)
7 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:226823

REFERENCE 2: 135:127220

REFERENCE 3: 135:127219

REFERENCE 4: 134:56541

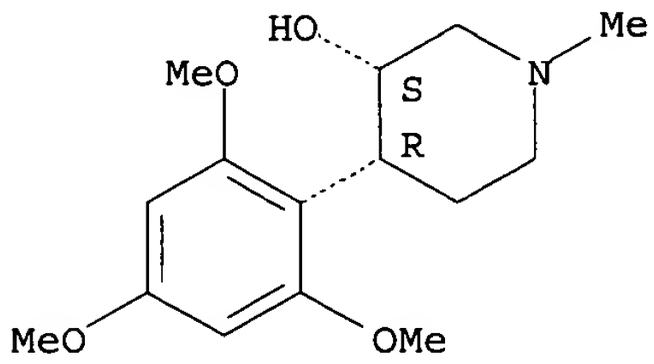
REFERENCE 5: 128:270537

REFERENCE 6: 110:8445

REFERENCE 7: 109:37739

L2 ANSWER 7 OF 10 REGISTRY COPYRIGHT 2002 ACS
RN **113225-19-7** REGISTRY
CN 3-Piperidinol, 1-methyl-4-(2,4,6-trimethoxyphenyl)-, (3S,4R)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3-Piperidinol, 1-methyl-4-(2,4,6-trimethoxyphenyl)-, cis-(-)-
FS STEREOSEARCH
MF C15 H23 N O4
CI COM
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, TOXCENTER, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

8 REFERENCES IN FILE CA (1967 TO DATE)
8 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:127220

REFERENCE 2: 135:127219

REFERENCE 3: 134:56541

REFERENCE 4: 132:35617

REFERENCE 5: 131:129906

REFERENCE 6: 128:270537

REFERENCE 7: 110:8445

REFERENCE 8: 109:37739

L2 ANSWER 8 OF 10 REGISTRY COPYRIGHT 2002 ACS
RN **9026-43-1** REGISTRY
CN Kinase (phosphorylating), protein serine/threonine (9CI) (CA INDEX NAME)
OTHER NAMES:
CN ATP-protein transphosphorylase
CN Cytidine 3',5'-cyclic monophosphate-responsive protein kinase
CN E.C. 2.7.1.37
CN Kinase (phosphorylating), protein
CN Phosphoprotein kinase
CN Protein kinase
CN Protein kinase (phosphorylating)
CN Protein phosphokinase
CN Protein serine kinase
CN Protein serine/threonine kinase
CN Serine kinase
CN Serine protein kinase
CN Serine/threonine kinase
CN Serine/threonine phosphokinase
CN Serine/threonine protein kinase
CN Serine/threonine-specific protein kinase
CN Threonine protein kinase
DR 121855-01-4, 121855-02-5, 122007-71-0, 122544-57-4, 123057-66-9, 123175-71-3, 129430-48-4, 139074-23-0, 144999-29-1, 143515-33-7, 117056-44-7, 117277-98-2, 117590-74-6
MF Unspecified
CI MAN
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CAPLUS, CEN, CHEMCATS, CIN, CSCHEM, EMBASE, IFICDB, IFIPAT, IFIUDB, PROMT, TOXCENTER, TOXLIT, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
22430 REFERENCES IN FILE CA (1967 TO DATE)
62 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
22437 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 136:67938

REFERENCE 2: 136:66992

REFERENCE 3: 136:64972

REFERENCE 4: 136:51014

REFERENCE 5: 136:50288

REFERENCE 6: 136:37505

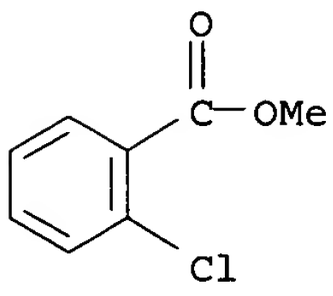
REFERENCE 7: 136:36358

REFERENCE 8: 136:34524

REFERENCE 9: 136:32466

REFERENCE 10: 136:32441

L2 ANSWER 9 OF 10 REGISTRY COPYRIGHT 2002 ACS
RN **610-96-8** REGISTRY
CN Benzoic acid, 2-chloro-, methyl ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Benzoic acid, o-chloro-, methyl ester (6CI, 7CI, 8CI)
OTHER NAMES:
CN Methyl 2-chlorobenzoate
CN Methyl o-chlorobenzoate
FS 3D CONCORD
MF C8 H7 Cl O2
CI COM
LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CSCHEM, GMELIN*, HODOC*, IFICDB, IFIPAT, IFIUDB, SPECINFO, TOXCENTER, TOXLIT, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

132 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
132 REFERENCES IN FILE CAPLUS (1967 TO DATE)
19 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 135:195365

REFERENCE 2: 135:127220

REFERENCE 3: 135:127219

REFERENCE 4: 135:60900

REFERENCE 5: 134:366704

REFERENCE 6: 134:178321

REFERENCE 7: 134:100624

REFERENCE 8: 133:321694

REFERENCE 9: 133:309799

REFERENCE 10: 133:119881

AN 2001:545692 CAPLUS
DN 135:127220
TI Preparation of ethanol solvate of Flavopiridol for cancer treatment
IN Kesseler, Kurt M.
PA Aventis Pharmaceuticals Inc., USA
SO PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001053294	A1	20010726	WO 2001-US520	20010108
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	BR 2001007724	A	20021001	BR 2001-7724	20010108
	EP 1252155	A1	20021030	EP 2001-902993	20010108
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	US 2001051638	A1	20011213	US 2001-760590	20010116
	NO 2002003385	A	20020827	NO 2002-3385	20020712
PRAI	US 2000-487815	A2	20000118		
	US 2000-287593P	P	20000118		
	WO 2001-US520	W	20010108		

AB An ethanol solvate form of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one (Flavopiridol, Form II), a method of making Form II and a compn. comprising Form II are described. The Form II was prepd. using (-)-cis-1-methyl-4R-(2,4,6-trimethoxyphenyl)-3S-piperidinol as the starting compd. Since Flavopiridol is useful in treating a no. of conditions or diseases that benefit from inhibition of protein kinases, and more particularly cyclin-dependent kinases, including cancer, the Form II is useful for prepn. of a pharmaceutical compn. for treating cancer.

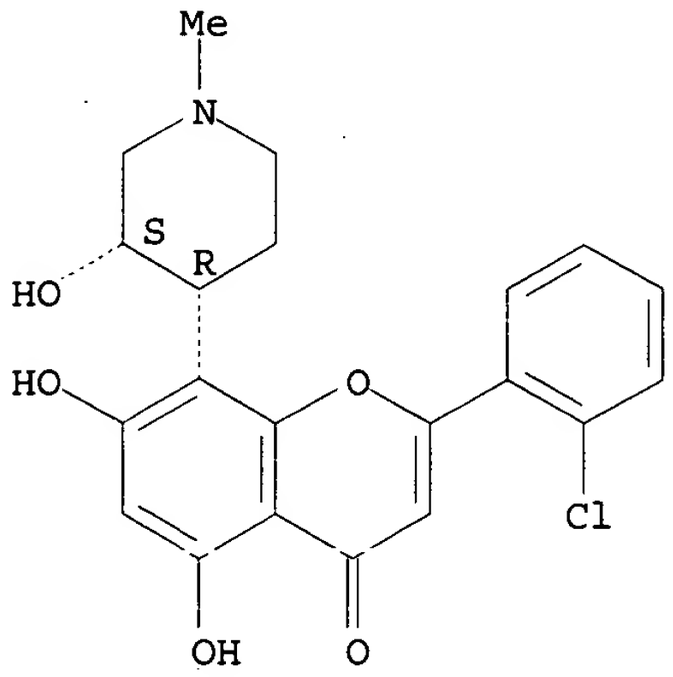
IT **351184-37-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn., properties and compns. of ethanol solvate of Flavopiridol for cancer treatment)

RN 351184-37-7 CAPLUS
CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-, hydrochloride, compd. with ethanol (9CI) (CA INDEX NAME)

CM 1

CRN 131740-09-5
CMF C21 H20 Cl N O5 . Cl H

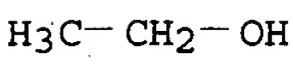
Absolute stereochemistry. Rotation (-).



● HCl

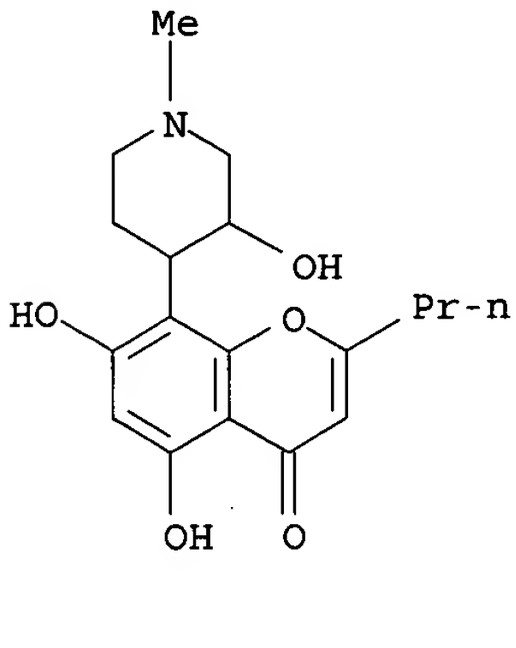
CM 2

CRN 64-17-5
CMF C2 H6 O



RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN **113225-03-9** REGISTRY
CN **4H-1-Benzopyran-4-one, 5,7-dihydroxy-8-(3-hydroxy-1-methyl-4-piperidinyl)-2-propyl-, hydrochloride (9CI)** (CA INDEX NAME)
MF C18 H23 N O5 . Cl H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 109:37739

AN 2001:545692 CAPLUS
DN 135:127220
TI Preparation of ethanol solvate of Flavopiridol for cancer treatment
IN Kesseler, Kurt M.
PA Aventis Pharmaceuticals Inc., USA
SO PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001053294	A1	20010726	WO 2001-US520	20010108
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	BR 2001007724	A	20021001	BR 2001-7724	20010108
	EP 1252155	A1	20021030	EP 2001-902993	20010108
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2003520798	T2	20030708	JP 2001-553768	20010108
	US 2001051638	A1	20011213	US 2001-760590	20010116
	NO 2002003385	A	20020827	NO 2002-3385	20020712
PRAI	US 2000-487815	A2	20000118		
	US 2000-287593P	P	20000118		
	WO 2001-US520	W	20010108		

AB An ethanol solvate form of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one (Flavopiridol, Form II), a method of making Form II and a compn. comprising Form II are described. The Form II was prepd. using (-)-cis-1-methyl-4R-(2,4,6-trimethoxyphenyl)-3S-piperidinol as the starting compd. Since Flavopiridol is useful in treating a no. of conditions or diseases that benefit from inhibition of protein kinases, and more particularly cyclin-dependent kinases, including cancer, the Form II is useful for prepn. of a pharmaceutical compn. for treating cancer.

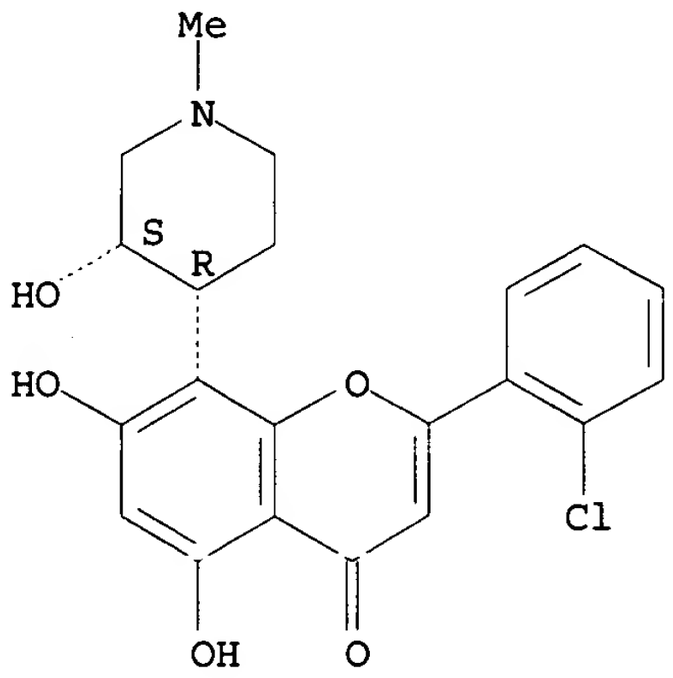
IT **351184-37-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn., properties and compns. of ethanol solvate of Flavopiridol for cancer treatment)

RN 351184-37-7 CAPLUS
CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-, hydrochloride, compd. with ethanol (9CI) (CA INDEX NAME)

CM 1

CRN 131740-09-5
CMF C21 H20 Cl N O5 . Cl H

Absolute stereochemistry. Rotation (-).



● HCl

CM 2

CRN 64-17-5
CMF C2 H6 O

H_3C-CH_2-OH

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

2/5/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11669395 BIOSIS NO.: 199800451126
Determination of flavopiridol (L86 8275; NSC 649890) in human plasma by reversed-phase liquid chromatography with electrochemical detection.
AUTHOR: Stinson Sherman F(a); Hill Kimberly; Siford Timothy J; Phillips Lawrence R; Daw Tracy W
AUTHOR ADDRESS: (a)Lab. Drug Discovery Res. Dev., Dev. Therap. Program, Div. Cancer Treat. Diagn. Cent., Natl. Canc**USA
JOURNAL: Cancer Chemotherapy and Pharmacology 42 (4):p261-265 Sept., 1998
ISSN: 0344-5704
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Purpose: Flavopiridol is a flavone which inhibits several cyclin-dependent kinases, and exhibits potent growth-inhibitory activity against a number of human tumor cell lines both in vitro, and when grown as xenografts in mice. It is currently being evaluated in a phase I clinical trial at the National Cancer Institute. The objective of this project was to develop and validate an analytical method for the assay of flavopiridol in human plasma, with sufficient sensitivity to permit the plasma pharmacokinetics of flavopiridol to be studied during clinical trials. Methods: Flavopiridol was isolated from human plasma samples by extraction with t-butylmethyl ether following alkalinization with borate buffer (pH 8.0). The extract was evaporated, the residue was dissolved in mobile phase, and analyzed by reversed-phase high-pressure liquid chromatography. Chromatography was accomplished with a polymer-based C18 column eluted with a mobile phase consisting of **methanol**-phosphate buffer, pH 11.0 (53:47 v/v). Electrochemical detection (ECD) was employed. Results: **Flavopiridol** was recovered from human plasma with an efficiency of 85-87%. Calibration curves were linear over the concentration range 10-500 nM (4.4219 ng/ml). Plasma standard concentrations were measured with an accuracy and precision ranging from 3.2% to 10%. Regression analysis of flavopiridol concentrations of 15 clinical trial plasma samples ranging in concentration from approximately 50 to 4000 muM quantitated by both ECD and mass spectrometry showed close agreement. The equation of the regression line was y = 1.02x + 8 with a correlation coefficient of 0.969. Continuous infusion of flavopiridol in four patients for 72 h at a rate of 50 mg/m2 per day, resulted in mean steady-state plasma concentrations of from 200 to 300 nM. Levels declined in a biexponential manner following termination of the infusion, falling to approximately 10 nM after 48 h. Conclusions: An analytical method for the assay of flavopiridol in human plasma was developed with sensitivity to at least 10 nM. The assay is accurate, precise and specific, and is suitable for determination of plasma flavopiridol concentrations for pharmacokinetic studies during clinical trials.

REGISTRY NUMBERS: 146426-40-6: FLAVOPIRIDOL; 146426-40-6: L86 8275
DESCRIPTORS:
MAJOR CONCEPTS: Oncology (Human Medicine, Medical Sciences); Pharmacology
BIOSYSTEMATIC NAMES: Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGANISMS: human (Hominidae)--patient
BIOSYSTEMATIC CLASSIFICATION (SUPER TAXA): Animals; Chordates; Humans; Mammals; Primates; Vertebrates
DISEASES: cancer--drug treatment, neoplastic disease
CHEMICALS & BIOCHEMICALS: flavopiridol {L-86-8275}--NSC-649890, plasma level determination, antineoplastic-drug
METHODS & EQUIPMENT: reversed-phase liquid chromatography--analytical method

CONCEPT CODES:

24008	Neoplasms and Neoplastic Agents-Therapeutic Agents; Therapy
10006	Clinical Biochemistry; General Methods and Applications
13002	Metabolism-General Metabolism; Metabolic Pathways
22002	Pharmacology-General
22003	Pharmacology-Drug Metabolism; Metabolic Stimulators
22005	Pharmacology-Clinical Pharmacology (1972-)
10050	Biochemical Methods-General
10060	Biochemical Studies-General
10504	Biophysics-General Biophysical Techniques
12512	Pathology, General and Miscellaneous-Therapy (1971-)
15002	Blood, Blood-Forming Organs and Body Fluids-Blood and Lymph Studies

BIOSYSTEMATIC CODES:

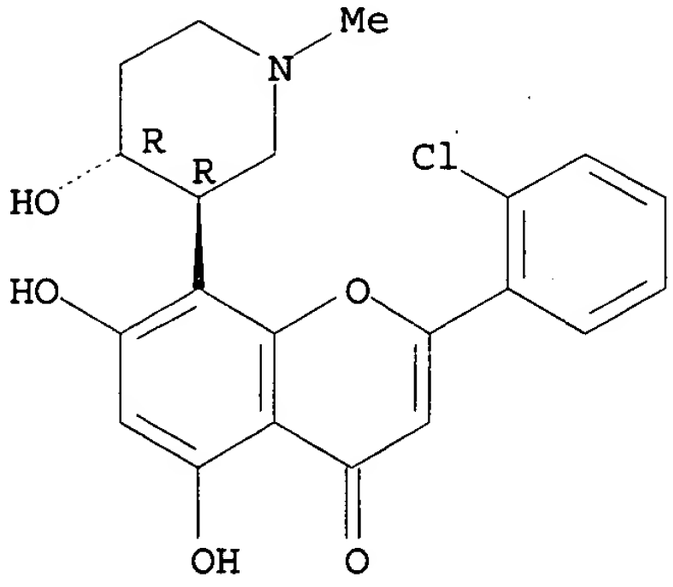
86215	Hominidae

L10 6 L9 AND PIPERIDIN?

=> d 1-6

L10 ANSWER 1 OF 6 REGISTRY COPYRIGHT 2002 ACS
RN 288155-43-1 REGISTRY
CN **4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3R,4R)-4-hydroxy-1-methyl-3-piperidinyl]-, rel- (9CI)** (CA INDEX NAME)
FS STEREOSEARCH
MF **C21 H20 Cl N O5**
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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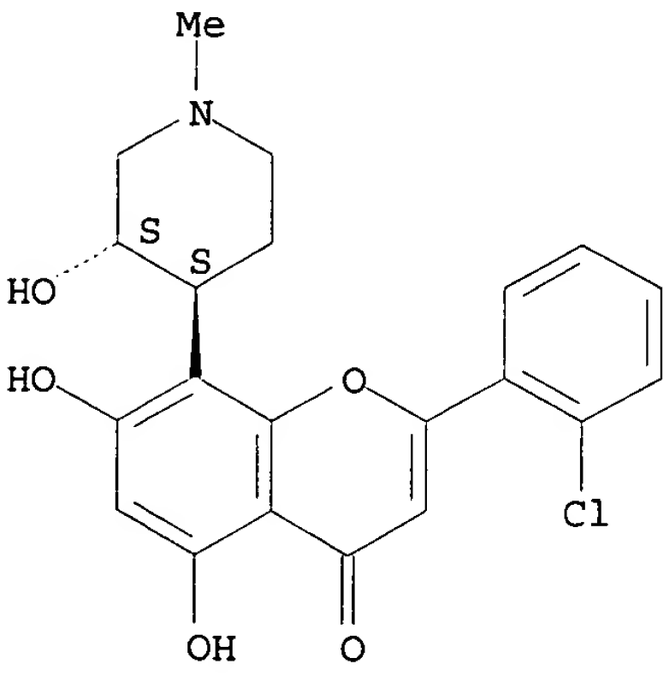
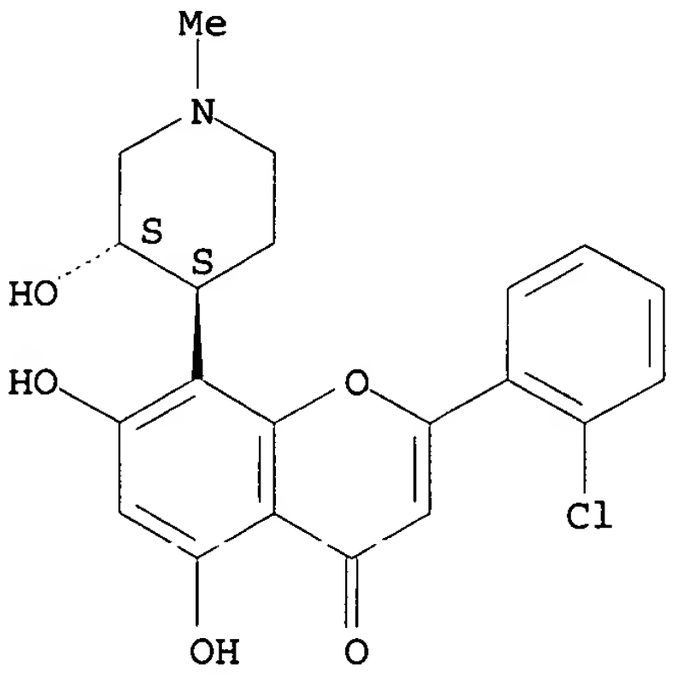
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L10 ANSWER 2 OF 6 REGISTRY COPYRIGHT 2002 ACS
RN 288155-39-5 REGISTRY
CN **4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3R,4R)-3-hydroxy-1-methyl-4-piperidinyl]-, rel- (9CI)** (CA INDEX NAME)
FS STEREOSEARCH
MF **C21 H20 Cl N O5**
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Relative stereochemistry.

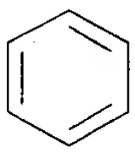




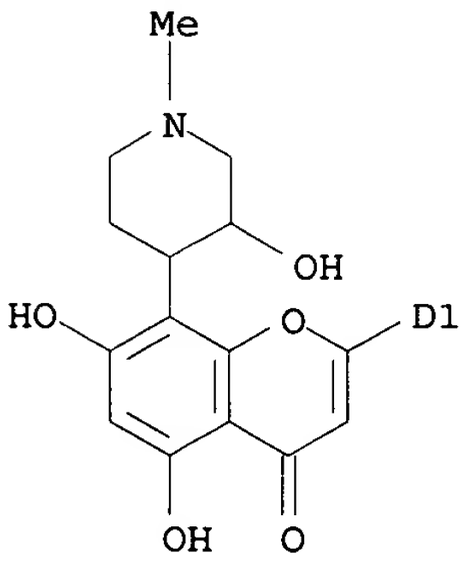
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L10 ANSWER 3 OF 6 REGISTRY COPYRIGHT 2002 ACS
RN 287397-10-8 REGISTRY
CN **4H-1-Benzopyran-4-one, 2-(chlorophenyl)-5,7-dihydroxy-8-(3-hydroxy-1-methyl-4-piperidinyl)- (9CI)** (CA INDEX NAME)
MF **C21 H20 Cl N O5**
CI IDS
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER



D1—Cl

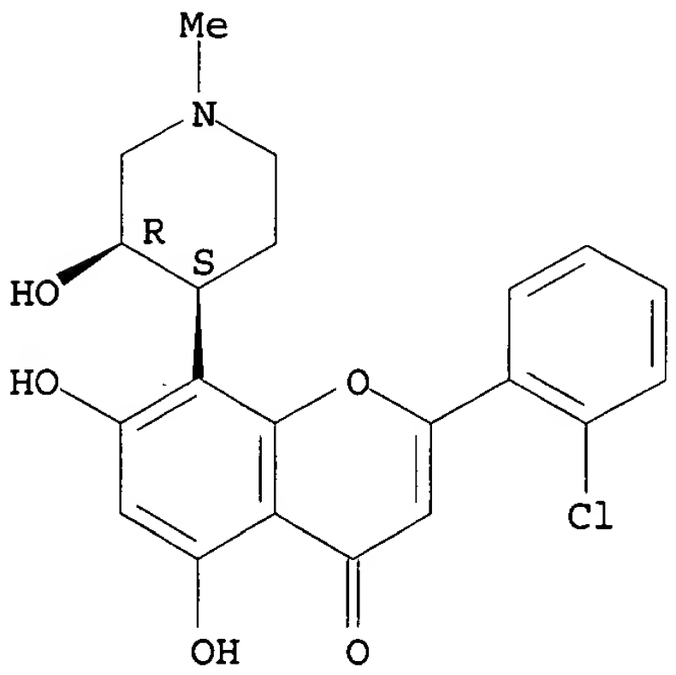


1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L10 ANSWER 4 OF 6 REGISTRY COPYRIGHT 2002 ACS

RN 244231-67-2 REGISTRY
CN **4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3R,4S)-3-hydroxy-1-methyl-4-piperidinyl]-, rel- (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN (.+-.)-Flavopiridol
CN (.+-.)-L 86-8275
FS STEREOSEARCH
MF **C21 H20 Cl N O5**
CI COM
SR CA
LC STN Files: CA, CAPLUS, CASREACT, TOXCENTER

Relative stereochemistry.

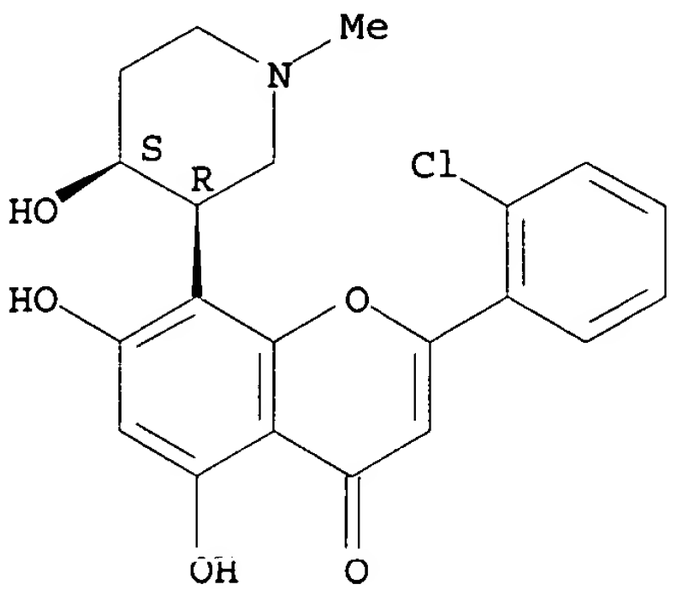


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1962 TO DATE)
3 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L10 ANSWER 5 OF 6 REGISTRY COPYRIGHT 2002 ACS
RN 190972-94-2 REGISTRY
CN **4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3R,4S)-4-hydroxy-1-methyl-3-piperidinyl]-, rel- (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-(4-hydroxy-1-methyl-3-piperidinyl)-, cis-**
FS STEREOSEARCH
MF **C21 H20 Cl N O5**
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Relative stereochemistry.



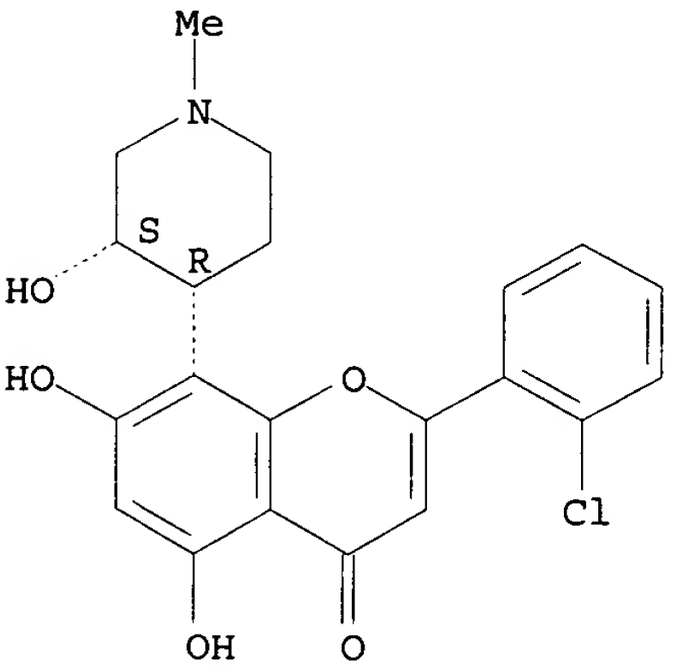
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1962 TO DATE)

2 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L10 ANSWER 6 OF 6 REGISTRY COPYRIGHT 2002 ACS
RN 146426-40-6 REGISTRY
CN **4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]- (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-(3-hydroxy-1-methyl-4-piperidinyl)-, cis-(-)-**
OTHER NAMES:
CN Flavopiridol
CN HMR 1275
CN L 86-8275
FS STEREOSEARCH
DR 358739-39-6
MF **C21 H20 Cl N O5**
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

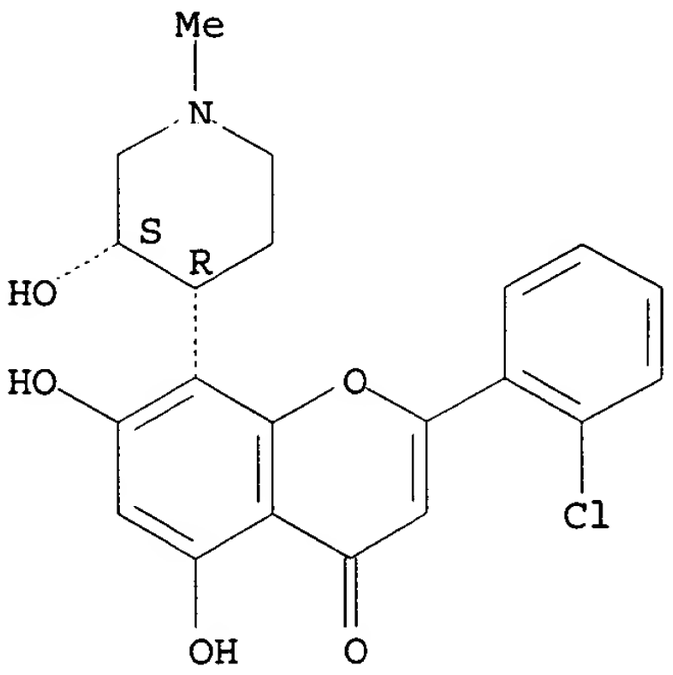
158 REFERENCES IN FILE CA (1962 TO DATE)
12 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
159 REFERENCES IN FILE CAPLUS (1962 TO DATE)

IN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-, hydrochloride, compd. with ethanol (9CI)

MF C21 H20 Cl N O5 . x C2 H6 O . Cl H

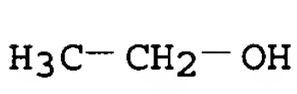
CM 1

Absolute stereochemistry. Rotation (-).



● HCl

CM 2

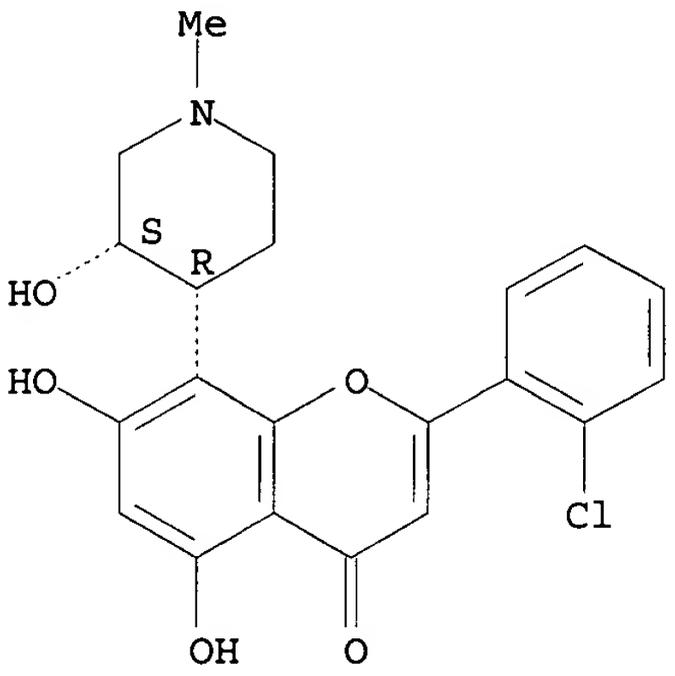


IN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-, hydrochloride, compd. with ethanol, hydrate (9CI)

MF C21 H20 Cl N O5 . x C2 H6 O . Cl H . x H2 O

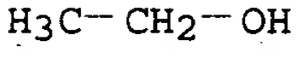
CM 1

Absolute stereochemistry. Rotation (-).



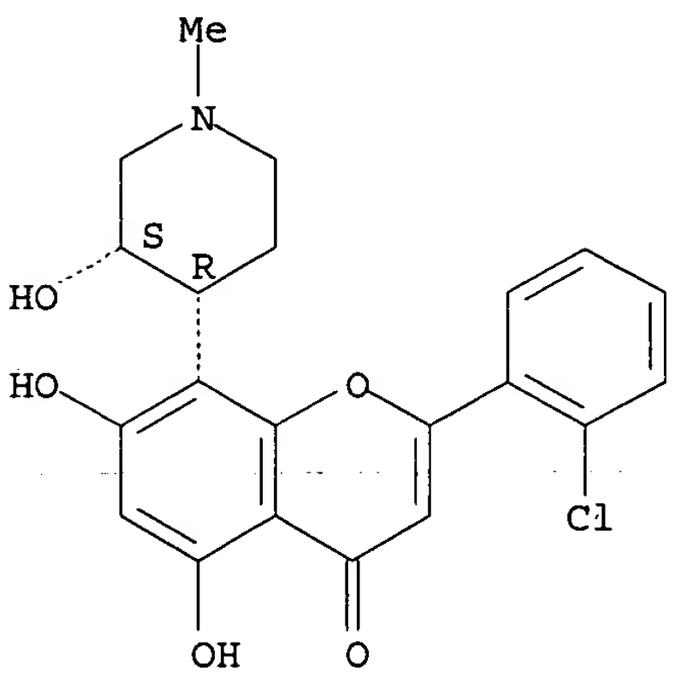
● HCl

CM 2



L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN 146426-40-6 REGISTRY
CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-(3-hydroxy-1-methyl-4-piperidinyl)-, cis-(-)-
OTHER NAMES:
CN **Flavopiridol**
CN HMR 1275
CN L 86-8275
FS STEREOSEARCH
MF C21 H20 Cl N O5
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, SYNTHLINE, TOXCENTER, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (-).



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L4           2 L1(L)ETHANOL

=> d bib abs 1-2

L4   ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2001 ACS
AN   2001:545692  CAPLUS
DN   135:127220
TI   Preparation of ethanol solvate of Flavopiridol for cancer treatment
IN   Kesseler, Kurt M.
PA   Aventis Pharmaceuticals Inc., USA
SO   PCT Int. Appl., 14 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.         KIND  DATE          APPLICATION NO.   DATE
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PI   WO 2001053294      A1    20010726      WO 2001-US520     20010108
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             CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
             HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
             LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
             SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
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             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     US 2001051638      A1    20011213      US 2001-760590    20010116
PRAI US 2000-487815     A2    20000118
     US 2000-287593     P     20000118
AB   An ethanol solvate form of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-
     (3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one (Flavopiridol,
     Form II), a method of making Form II and a compn. comprising Form II are
     described.  The Form II was prepd. using (-)-cis-1-methyl-4R-(2,4,6-
     trimethoxyphenyl)-3S-piperidinol as the starting compd.  Since
     Flavopiridol is useful in treating a no. of conditions or diseases that
     benefit from inhibition of protein kinases, and more particularly
     cyclin-dependent kinases, including cancer, the Form II is useful for
     prepn. of a pharmaceutical compn. for treating cancer.
RE.CNT  2
RE
(1) Hoechst AG; EP 0366061 A 1990 CAPLUS
(2) Kattige, S; US 4900727 A 1990 CAPLUS

L4   ANSWER 2 OF 2  CAPLUS  COPYRIGHT 2001 ACS
AN   1999:213255  CAPLUS
DN   131:35767
TI   Solubilization of Ionized and Un-ionized Flavopiridol by Ethanol and
     Polysorbate 20
AU   Li, Ping; Tabibi, S. Esmail; Yalkowsky, Samuel H.
CS   Department of Pharmaceutical Sciences College of Pharmacy, University of
     Arizona, Tucson, AZ, 85721, USA
SO   J. Pharm. Sci. (1999), 88(5), 507-509
     CODEN: JPMSAE; ISSN: 0022-3549
PB   American Chemical Society
DT   Journal
LA   English
AB   Because the ionized species is more polar than its unionized counterpart,
     it is often assumed that the ionized species of the drug does not make a
     meaningful contribution to solubilization by either cosolvents or
     surfactants.  This report extends previous studies on solubilization of
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the ionic species by a combination of pH control and complexation to pH control and micellization and to pH control and cosolvency. The total aq. soly. is expressed as the addn. of the concn. of all contributing species: free un-ionized drug [Du], free ionized drug [Di], un-ionized drug micelle [DuM], and ionized drug micelle [DiM] for surfactant, and free un-ionized drug [Dcu] and free ionized drug [Dci] for cosolvent. The equations indicate that under certain conditions the ionized species can be more important in detg. the drug total soly. than the unionized species. Flavopiridol, a weak base, is used to test these newly generated equations. As expected, the micellar partition coeff. and solubilization power for ionized flavopiridol are both less than those of the un-ionized species. However, at acidic pH, the solubilities of the ionized drug in surfactant micelles [DiM] and in cosolvent-water [Dci] are both much greater than that of the unionized drug. This difference is because the solubilization of the ionized drug is proportional to its aq. soly., and its soly. [Di] can be as much as 24-fold greater than that of the free un-ionized species [Du].

RE.CNT 8

RE

(1) Alvarez-Nunez, F; PDA J Pharm Sci Technol 1998, V52, P33 MEDLINE
(4) Johnson, M; J Pharm Sci 1994, V83, P1142 CAPLUS
(5) Li, P; J Pharm Sci 1998, V87, P1535 CAPLUS
(7) Okimoto, K; Pharm Res 1996, V13, P256 CAPLUS
(8) Tinwalla, A; Pharm Res 1993, V10, P1136 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> s l1/p
L13             9 L1/P

=> d bib abs 1-9

L13  ANSWER 1 OF 9  CAPLUS  COPYRIGHT 2001 ACS
AN   2001:545692  CAPLUS
DN   135:127220
TI   Preparation of ethanol solvate of Flavopiridol for cancer treatment
IN   Kesseler, Kurt M.
PA   Aventis Pharmaceuticals Inc., USA
SO   PCT Int. Appl., 14 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.         KIND  DATE           APPLICATION NO.   DATE
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PI   WO 2001053294       A1   20010726       WO 2001-US520     20010108
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             CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
             HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
             LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
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             BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     US 2001051638      A1   20011213       US 2001-760590    20010116
PRAI US 2000-487815     A2   20000118
     US 2000-287593     P    20000118
AB   An ethanol solvate form of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-
     (3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one (Flavopiridol,
     Form II), a method of making Form II and a compn. comprising Form II are
     described.  The Form II was prepd. using (-)-cis-1-methyl-4R-(2,4,6-
     trimethoxyphenyl)-3S-piperidinol as the starting compd.  Since
     Flavopiridol is useful in treating a no. of conditions or diseases that
     benefit from inhibition of protein kinases, and more particularly
     cyclin-dependent kinases, including cancer, the Form II is useful for
     prepn. of a pharmaceutical compn. for treating cancer.
RE.CNT  2
RE
(1) Hoechst AG; EP 0366061 A 1990 CAPLUS
(2) Kattige, S; US 4900727 A 1990 CAPLUS

L13  ANSWER 2 OF 9  CAPLUS  COPYRIGHT 2001 ACS
AN   2001:545691  CAPLUS
DN   135:127219
TI   Preparation of pseudopolymorph of Flavopiridol
IN   Bafus, Gary L.; Harrison-Bowman, Christine M.; Silvey, Gary L.
PA   Aventis Pharmaceuticals Inc., USA
SO   PCT Int. Appl., 23 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.         KIND  DATE           APPLICATION NO.   DATE
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PI   WO 2001053293       A1   20010726       WO 2001-US519     20010108
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             HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
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SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 2000-484717 A2 20000118

AB Prepn. of a pseudopolymorph of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]- H-1-benzopyran-4-one hydrochloride (Flavopiridol HCl, Form I), essentially free of Form II (an ethanol solvate or hydrate), a pharmaceutical compn. comprising a therapeutically effective Form I and a carrier, and methods of using the pseudopolymorph for inhibiting protein kinases are described. For example, Flavopiridol Form I was prepd. by crystn. from Form II azeotropic mixt. with ketone, i.e., Me Et ketone, and filtration of crystd. Form I.

RE.CNT 3

RE

(1) Li, P; PDA J Pharm Sci Technol 1999, V53(3), P137 CAPLUS

(2) Naik, R; US 5284856 A 1994 CAPLUS

(3) Sedlacek; Int J Oncology V9, P1143 CAPLUS

L13 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2001 ACS

AN 2001:283821 CAPLUS

DN 134:316086

TI Manufacture of polyglutamate-therapeutic agent conjugates

IN Kumar, Anil M.; Klein, J. Peter; Bhatt, Rama; Vawter, Edward

PA Cell Therapeutics, Inc., USA

SO PCT Int. Appl., 44 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001026693	A2	20010419	WO 2000-US28109	20001012

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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-159135 P 19991012

AB The invention provides new processes for prepg. polyglutamic acid-therapeutic agent conjugates for clin. development and pharmaceutical use, and polyglutamic acid-therapeutic agent conjugates prepd. by these processes. Poly(L-glutamic acid) in N,N-dimethylformamide was reacted with paclitaxel in presence of N,N-diisopropylcarbodiimide to obtain poly-L-glutamic acid-2'-paclitaxel conjugate.

L13 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2001 ACS

AN 2001:128852 CAPLUS

DN 134:366704

TI A stereocontrolled approach to substituted piperidones and piperidines: flavopiridol D-ring analogs

AU Gross, A.; Borcherding, D. R.; Friedrich, D.; Sabol, J. S.

CS Aventis Pharmaceuticals Inc., Bridgewater, NJ, 08807-0800, USA

SO Tetrahedron Lett. (2001), 42(9), 1631-1633
CODEN: TELEAY; ISSN: 0040-4039

PB Elsevier Science Ltd.

DT Journal

LA English

AB A stereocontrolled approach to substituted piperidones and piperidines is

presented, and their utility as intermediates for the synthesis of flavopiridol D-ring analogs is described.

RE.CNT 7

RE

(1) Gonzalez, F; Org Synth 1986, V64, P175 CAPLUS
(2) Johnson, W; J Am Chem Soc 1970, V92, P741 CAPLUS
(3) Kattige, S; US 4900727 1990 CAPLUS
(4) Naik, R; US 5284856 1988 CAPLUS
(5) Naik, R; Tetrahedron 1988, V44, P2081 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2001 ACS
AN 2000:727121 CAPLUS
DN 134:56541
TI Thio- and Oxoflavopiridols, Cyclin-Dependent Kinase 1-Selective Inhibitors: Synthesis and Biological Effects
AU Kim, Kyoung Soon; Sack, John S.; Tokarski, John S.; Qian, Ligang; Chao, Sam T.; Leith, Leslie; Kelly, Yolanda F.; Misra, Raj N.; Hunt, John T.; Kimball, S. David; Humphreys, William G.; Wautlet, Barris S.; Mulheron, Janet G.; Webster, Kevin R.
CS Departments of Oncology Chemistry Oncology Drug Discovery Structural Biology and Modelling and Metabolism and Pharmacokinetics, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ, 08543-4000, USA
SO J. Med. Chem. (2000), 43(22), 4126-4134
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
OS CASREACT 134:56541
AB Flavopiridol analogs, thio- and oxoflavopiridols which contain a sulfur or oxygen atom linker between a chromone ring and the hydrophobic side chain, are selective cyclin-dependent kinase 1 (CDK1) inhibitors with an IC50 of 110 and 130 nM. Dynamic kinetic resoln. of the racemate gave the intermediate (+)-(R)-1-methyl-4-(2,4,6-trimethoxyphenyl)-3-piperidinone which was reduced to give (3S,4R)-1-methyl-4-(2,4,6-trimethoxyphenyl)-3-piperidinol. One of the target compds. thus prepd. was (-)-2-[(2-chlorophenyl)thio]-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-4H-1-benzopyran-4-one hydrochloride. Hydrophobic side chains such as chlorophenyl or tert-Bu produced potent CDK1 inhibitory activity, while hydrophilic side chains such as pyrimidine or aniline caused a severe redn. in CDK inhibitory activity. These analogs are competitive inhibitors with respect to ATP, and therefore activity was dependent upon the CDK subunit without being affected by the cyclin subunit or protein substrate. Some thio- and oxoflavopiridols are not only selective within the CDK family but also discriminated between unrelated serine/threonine and tyrosine protein kinases. CDK1 selective thio- and oxoflavopiridol analogs inhibit the colony-forming ability of multiple human tumor cell lines and possess a unique antiproliferative profile in comparison to flavopiridol.

RE.CNT 41

RE

(1) Abraham, R; Biol Cell 1995, V83, P105 CAPLUS
(2) Bairoch, A; Nucleic Acids Res 2000, V28, P45 CAPLUS
(4) Burley, S; FEBS Lett 1986, V203, P139 CAPLUS
(5) Carlson, B; Cancer Res 1996, V56, P2973 CAPLUS
(6) de Azevedo, W; Proc Natl Acad Sci U S A 1996, V93, P2735 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2001 ACS
AN 1998:494641 CAPLUS
DN 129:227384
TI Exploiting chemical libraries, structure, and genomics in the search for kinase inhibitors
AU Gray, Nathanael S.; Wodicka, Lisa; Thunnissen, Andy-Mark W. H.; Norman,

Thea C.; Kwon, Soojin; Espinoza, F. Hernan; Morgan, David O.; Barnes, Georjana; LeClerc, Sophie; Meijer, Laurent; Kim, Sung-Hou; Lockhart, David J.; Schultz, Peter G.

CS Howard Hughes Med. Inst., Univ. California, Berkeley, CA, 94720, USA

SO Science (Washington, D. C.) (1998), 281(5376), 533-538
CODEN: SCIEAS; ISSN: 0036-8075

PB American Association for the Advancement of Science

DT Journal

LA English

AB Selective protein kinase inhibitors were developed on the basis of the unexpected binding mode of 2,6,9-trisubstituted purines to the ATP-binding site of the human cyclin-dependent kinase 2 (CDK2). By iterating chem. library synthesis and biol. screening, potent inhibitors of the human CDK2-cyclin A kinase complex and of Saccharomyces cerevisiae Cdc28p were identified. The structural basis for the binding affinity and selectivity was detd. by anal. of a three-dimensional crystal structure of a CDK2-inhibitor complex. The cellular effects of these compds. were characterized in mammalian cells and yeast. In the latter case the effects were characterized on a genome-wide scale by monitoring changes in mRNA levels in treated cells with high-d. oligonucleotide probe arrays. Purine libraries could provide useful tools for analyzing a variety of signaling and regulatory pathways and may led to the development of new therapeutics.

L13 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2001 ACS

AN 1998:208527 CAPLUS

DN 128:270537

TI Process for the preparation of chiral ketones as intermediates for flavopiridol and analogs

IN Kim, Kyoung Soon

PA Bristol-Myers Squibb Co., USA

SO PCT Int. Appl., 22 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

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PI	WO 9813344	A1	19980402	WO 1997-US16432	19970916
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	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
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	AU 9743517	A1	19980417	AU 1997-43517	19970916
PRAI	US 1996-26748		19960926		
	WO 1997-US16432		19970916		

OS CASREACT 128:270537; MARPAT 128:270537

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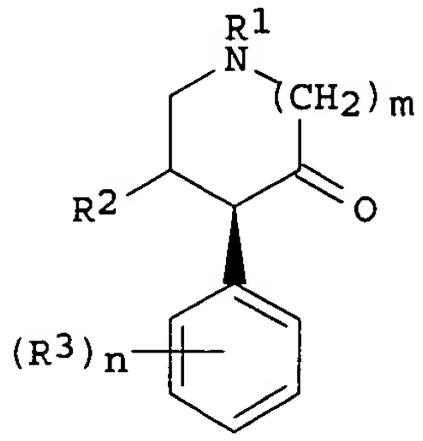

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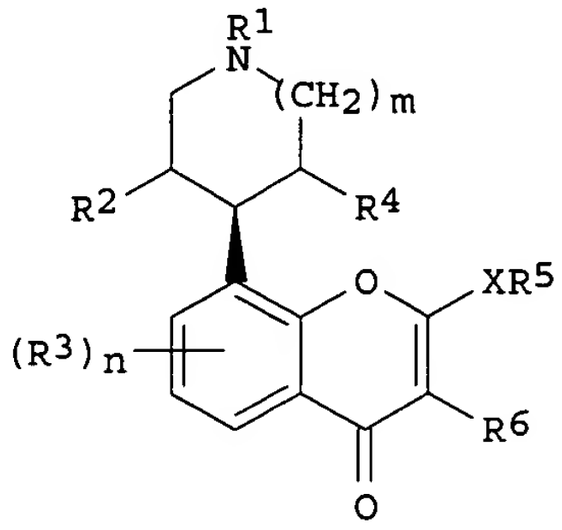

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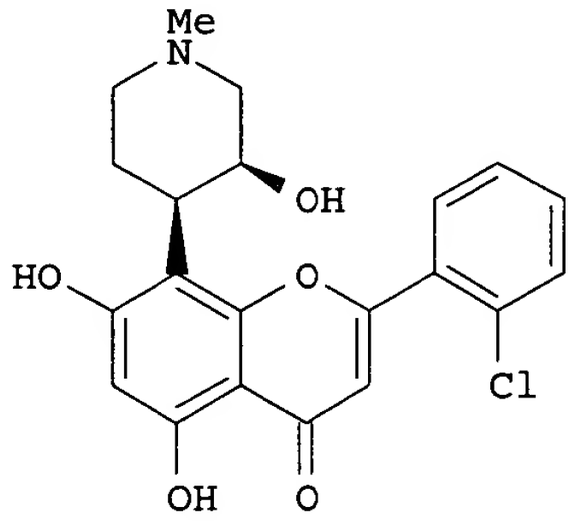


III

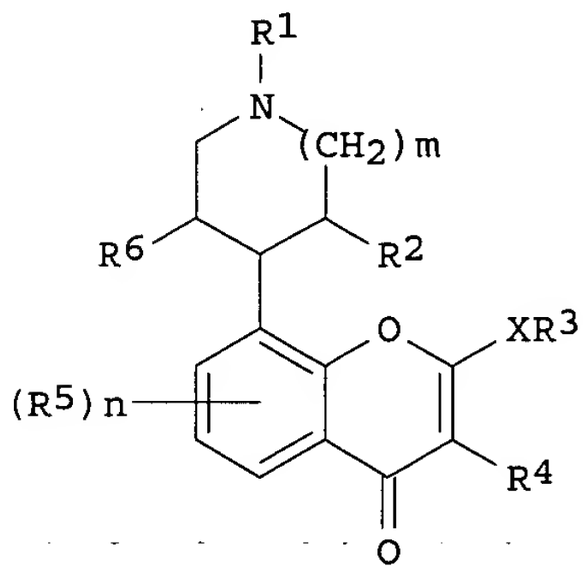
AB A process for prepg. chiral phenylpiperidones [I; R1 = H, (cyclo)alkyl, aryl(alkyl), alkylcarbonyl, (CH2)qNR7R8, etc.; R2 = H, OH, halo, alkoxy, carboxy, (cyclo)alkyl, aryl(alkyl), alkylcarbonyloxy, alkylthio, NR7R8, etc.; R3 = H, OH, alkoxy, (cyclo)alkyl, aryl(alkyl), aryloxy, CHO, etc.; R7, R8 = H, (cyclo)alkyl, aryl(alkyl), heterocyclyl, etc.; R7R8N may form a hetero ring; m = 0-2; n = 1-3; q = 2-5] and piperidinylbenzopyranones [II; R1-R3, m, n, q as above; R4 = H, OH, alkoxy, (cyclo)alkyl, aryl(alkyl), amino, thiol, etc.; R5 = (cyclo)alkyl, aryl(alkyl), heterocyclyl(alkyl); R6 = H, OH, halo, alkyl, aryl(alkyl), NO2, amino, etc.; X = bond, O, S] and their pharmaceutically acceptable salts is claimed, comprising (a) salification of a racemic I with a chiral acid in an org. solvent and (b) treatment of the salt with an aq. base. Compds. I are useful as intermediates in the prepn. of protein kinase inhibitors. Thus, a mixt. of 1.60 g (.+-.)-1-methyl-4-(2,4,6-trimethoxyphenyl)-3-piperidinone and 2.28 g dibenzoyl-D-tartaric acid in 10 mL MeOH was heated at reflux under Ar and stirred overnight at the ambient temp. to give 2.89 g salt which was dissolved in a mixt. of 40 mL CH2Cl2 and 12 mL 0.5 N aq. NaOH, the org. phase was sepd. and worked up to give 1.60 g (R)-piperidone I (R1 = Me, R2 = H, (R3)3 = 2-, 4- and 6-MeO, m = 1) [m. 131-133, [.alpha.D] = +31.degree. (MeOH, c 1.0)]. This was subjected to redn. with (Me2CHCH2)2AlH, the resulting 3-piperidinol intermediate C-acetylated and partially demethylated with Ac2O and BF3.cntdot.THF in CH2Cl2 to give (3S-cis)-4-(3-acetyl-2-hydroxy-4,6-dimethoxyphenyl)-1-methyl-3-piperidinol which was cyclocondensed with Me 2-chlorobenzoate in presence of NaH in DMF and the resulting 2-(2-chlorophenyl)benzopyranone subjected to MeO ether cleavage with BBr3 in ClCH2CH2Cl to give cis-piperidinylbenzopyranone III.

L13 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2001 ACS
AN 1997:752833 CAPLUS
DN 128:34632
TI Preparation of 2-thia- or 2-oxa-flavopiridol analogs for use as protein kinase inhibitors
IN Kim, Kyoung Soon
PA Bristol-Myers Squibb Company, USA
SO PCT Int. Appl., 46 pp.

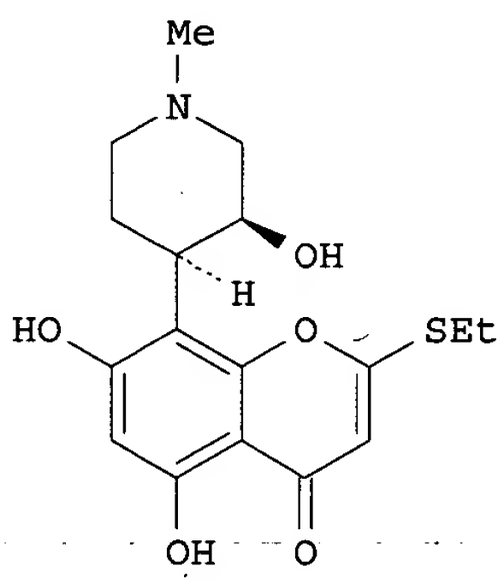
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9742949	A1	19971120	WO 1997-US7610	19970506
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9730594	A1	19971205	AU 1997-30594	19970506
PRAI	US 1996-17529		19960510		
	WO 1997-US7610		19970506		

OS MARPAT 128:34632
GI



I



II

AB Flavopiridol analogs I [X = S, O; R1 = H, alkyl, aryl, cycloalkyl, acyl, alkoxycarbonyl, aryloxycarbonyl; R2 = R6 = H, OH, SH, alkyl, aryl, cycloalkyl, alkoxy, aryloxy, alkoxycarbonyl, aryloxycarbonyl, amino, alkylthio, arylthio; R3 = alkyl, cycloalkyl, aryl, heterocyclyl; R4 = H, NO2, OH, alkyl, aryl, amino, halogen, alkoxy, carboxy, heterocyclyl, alkoxycarbonyl; R5 = H, OH, CHO, CN, NO2, halogen, alkyl, aryl, cycloalkyl, alkoxy, aryloxy, alkylcarbonyloxy, arylcarbonyloxy, carboxy, amino, alkylthio, alkylsulfinyl, carbamoyloxy; m = 0 - 3; n = 0 - 3] were prepd. for use as protein kinase inhibitors which are useful in the treatment of proliferative diseases, such as cancer, inflammation, or arthritis. Thus, II was prepd. starting from 1,3,5-trimethoxybenzene and 1-methyl-2-piperidone. The prepd. compds. were tested for cdk4/cyclin D1 kinase inhibition.

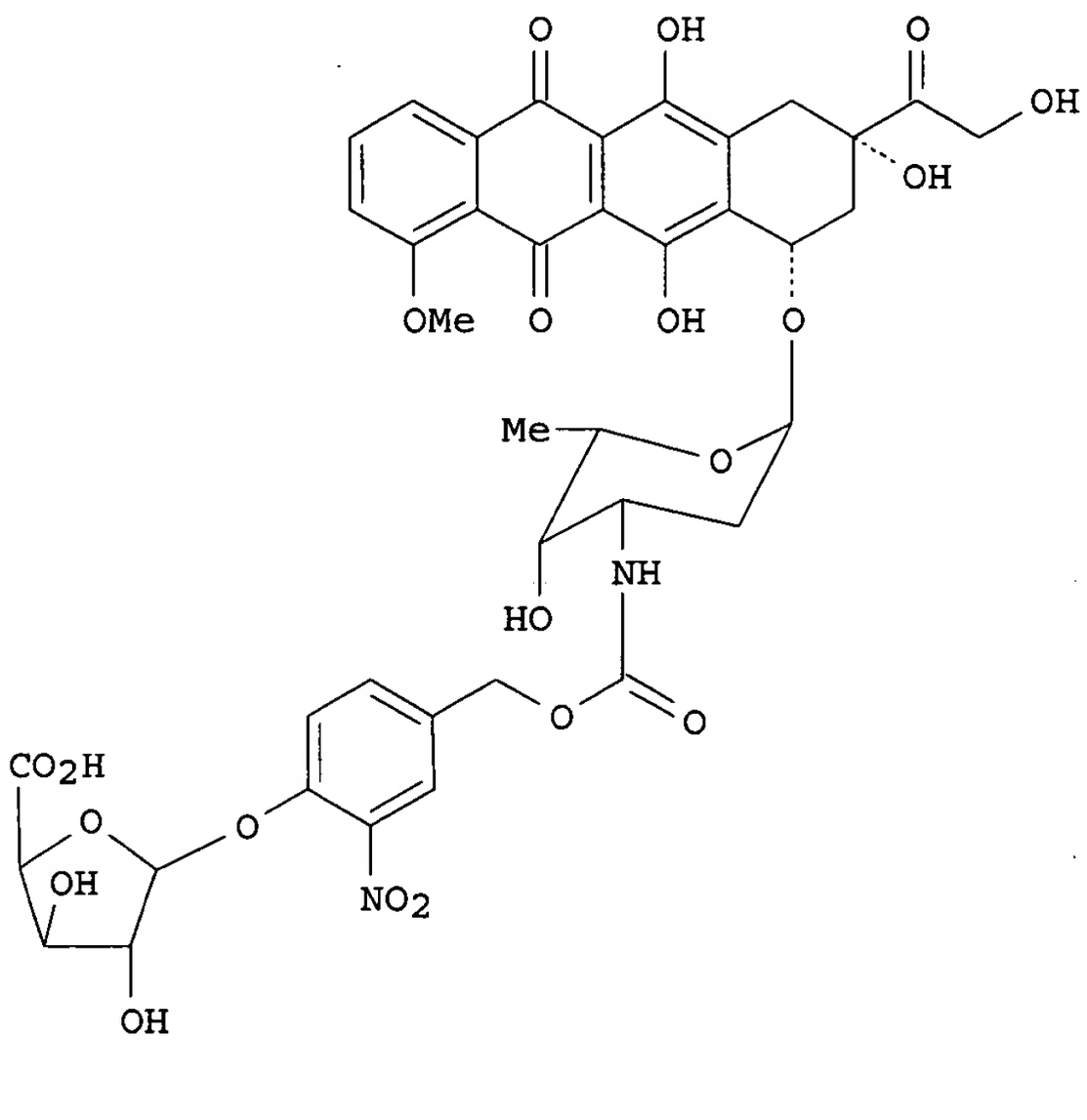
L13 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2001 ACS
AN 1995:826475 CAPLUS
DN 123:228772
TI Preparation of prodrugs for enzyme-mediated activation
IN Bosslet, Klaus; Czec, Joerg; Hoffmann, Dieter; Tillequin, Francois; Florent, Jean-Claude; Azoulay, Michel; Monneret, Claude; Jacquesy, Jean-Claude; Gesson, Jean-Pierre; Et, Al.
PA Behringwerke Aktiengesellschaft, Germany; Laboratories Hoechst S.A.
SO Eur. Pat. Appl., 14 pp.
CODEN: EPXXDW

DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 642799	A1	19950315	EP 1994-113388	19940826
	EP 642799	B1	20011107		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	EP 647450	A1	19950412	EP 1993-114475	19930909
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	AU 9471699	A1	19950323	AU 1994-71699	19940907
	AU 678494	B2	19970529		
	CA 2131662	AA	19950310	CA 1994-2131662	19940908
	NO 9403319	A	19950310	NO 1994-3319	19940908
	ZA 9406920	A	19950412	ZA 1994-6920	19940908
	JP 07149667	A2	19950613	JP 1994-214597	19940908
	US 5621002	A	19970415	US 1994-302459	19940909
PRAI	EP 1993-114475	A	19930909		
	DE 1992-4236237		19921027		

OS MARPAT 123:228772

GI



I

AB Enzymically cleavable prodrugs SZW (S = modified competitive enzyme inhibitor; W = pharmacol. active substance; Z = bond, self-immolative spacer group; such that the Z-S bond can be enzymically cleaved at a .gtoreq.2-fold lower Michaelis-Menten const.) (e.g., I), with reduced Michaelis-Menten consts., are prepd.

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Filed on 18 January 2000 (18.01.2000)

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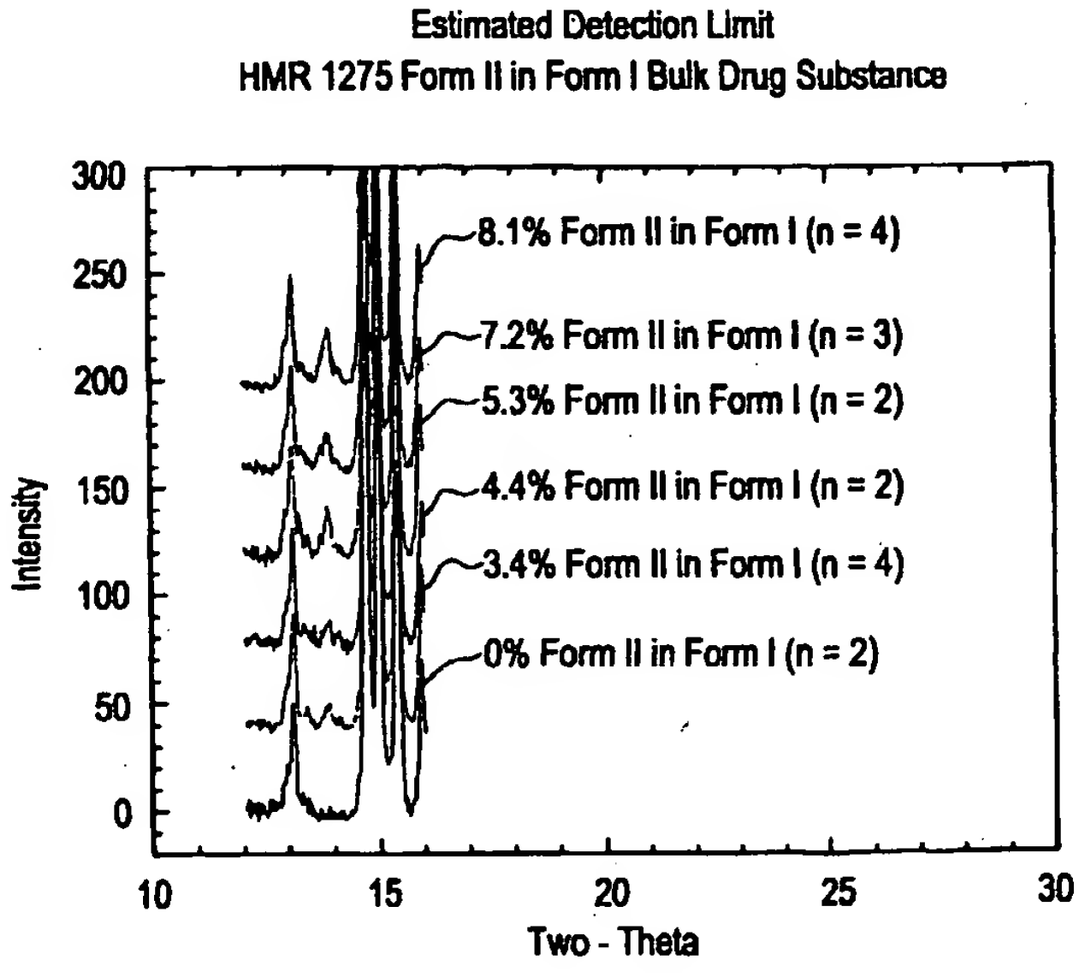
[Continued on next page]

(54) Title: PSEUDOPOLYMORPH OF (-)-CIS-2-(2-CHLOROPHENYL)-5,7-DIHYDROXY-8[4R-(3S-HYDROXY-1-METHYL)PIPERIDINYL]-4H-1-BENZOPYRAN-4-ONE



(57) Abstract: The present invention comprises a pseudopolymorph of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride, a method of making same, a pharmaceutical composition and methods of using the pseudopolymorph.

WO 01/53293 A1

patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Published:

— *with international search report*

Ps udop lymorph of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-m thyl)pip ridinyl]-4H-1-b nzopyran-4-one

BACKGROUND OF THE INVENTION

The compound (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one or one of its pharmaceutically acceptable salt forms (known as "Flavopiridol") is an immunomodulator and antiinflammatory agent (U. S. Patent no. 4,900,727), and inhibitor of oncogene-encoded kinases or growth factor receptor tyrosine kinases (US Patent no. 5,284,856). Flavopiridol is a strong inhibitor of cyclin dependent kinases (CDKs) including CDK1, CDK2, CDK4, CDK6 and CDK7, (cdk1/clyclin B; cdk2/cyclin A; cdk2/cyclin E; cdk4/cyclinD; cdk6/cyclinD; cdk7/cyclin H) with the potential to cause inhibition of cell cycle progression in G_1 and G_2 by multiple mechanisms relatable to cdk inhibition. See *International Journal of Oncology* 9: 1143-1168 (1996). Also, Flavopiridol has been shown to inhibit the EGF receptor family, the receptor associated SRC family kinases, and signal transducing kinases. In vitro and in vivo experiments have shown that Flavopiridol is able to inhibit a broad type range of human tumors, leukemias and lymphomas.

(-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one or a pharmaceutically acceptable salt thereof crystallizes into numerous solvates with solvents such as ethanol, DMSO, methanol, acetonitrile/isopropanol, ethanol/isopropanol, and isopropanol and solvate hydrates such as ethanol/ and isopropanol/water combinations. The preferred form is the Flavopiridol hydrochloride ethanol/water solvate form (hereafter "Form II").

Although Form II meets pharmaceutical standards, it has a tendency to absorb water if not packaged in water impermeable packaging, which increases cost of production. It is also desirable to have as much stability as possible in the crystalline structure for handling purpos s and for approvals through different pharmaceutical regulatory agencies throughout the world.

It is an object of the present invention to provide a form of Flavopiridol as Form I which has superior physical characteristics for us as a pharmaceutical composition.

SUMMARY OF THE INVENTION

The present invention comprises pseudopolymorph Form I as defined by x-ray powder diffraction. Preferably, Form I is essentially free of Form II and/or other Flavopiridol forms. It is useful in a pharmaceutical composition comprising an effective amount of Form I and a pharmaceutically acceptable carrier. Form I is useful as a protein kinase inhibitor, cyclin dependent kinase inhibitor, and in the treatment for various forms of cancer.

Form I is further characterized by its ability of being less hydroscopic than Form II e.g., has less weight gain due in comparative relative humidities.

Form is prepared by combining a sufficient quantity of Form II with a sufficient amount of an appropriate azeotropic solvent thus forming an azeotropic mixture; submitting the azeotropic mixture to azeotropic distillation sufficient to form Form I; and optionally recovering Form I therefrom.

DESCRIPTION OF DRAWING

Figure 1: Estimated Limit of Detection of Form II in Form I by X-ray Powder Diffraction (XRPD)

To estimate the limit of detection of Form II in Form I, varying quantities of Form II were accurately weighed and carefully mixed (unmilled) with Form I. The entire mixture was transferred to a platinum sample holder and leveled using glass microscope slide. All samples were scanned at 0.2°/min. from 12° - 16° 2_Θ. At a minimum, duplicate determinations were made at each spike level, the XRPD patterns averaged, and the peak height at ~13.8° 2_Θ measured to the nearest 0.1 mm. The estimated det ction limit of Form II in Form I is ~ 3%.

DETAILED DESCRIPTION OF THE INVENTION

"Form I" means (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride. It has the same active ingredient as Flavopiridol but differs from known crystals of Flavopiridol in that it is anhydrous and/or solvate free, i.e., a pseudopolymorph of known forms of Flavopiridol.

Form I is identified by x-ray diffraction patterns expressed in terms of "d" spacing using Cu K-alpha radiation as follows:

D space- Å
12.708
4.323
5.594
5.349
3.590,

and more preferably as:

D space- Å
12.708
4.323
5.594
5.349
3.590
3.366
4.209
3.395
3.438
4.839.

Also, Form I is identified by x-ray diffraction patterns expressed in terms of "d" spacing using Cu K-alpha radiation and the Relative Intensities thereof:

D space- Å	Relative Intensities
12.708	Strong
4.323	Strong
5.594	Strong
5.349	Medium
3.590	Medium
3.366	Medium
4.209	Medium
3.395	Medium
3.438	Medium
4.839	M dium.

More pref rably, Form I is identified x-ray diffraction patterns expressed in terms of "d" spacing using Cu K-alpha radiation and the Relativ Intensities (RI) p rcentages thereof:

D space- Å	Relative Intensity %
12.708	100.0
4.323	75.9
5.594	58.5
5.349	49.5
3.590	46.6
3.366	42.0
4.209	40.7
3.395	39.5
3.438	38.8
4.839	37.1.

Form I X-ray powder diffraction is more fully described in Table 1.

Table 1

2 Theta Angle (°)	D Space - Å	Relative Intensity	Relative Intensity (%)
6.950	12.708	Strong	100.0
20.529	4.323	Strong	75.9
15.830	5.594	Strong	58.5
16.560	5.349	Medium	49.5
24.778	3.590	Medium	46.6
26.457	3.366	Medium	42.0
21.091	4.209	Medium	40.7
26.226	3.395	Medium	39.5
25.898	3.438	Medium	38.8
18.320	4.839	Medium	37.1
8.308	10.634	Medium	35.7
23.748	3.744	Medium	33.4
13.010	6.799	Medium	32.4
30.520	2.927	Medium	31.0
27.106	3.287	Weak	26.2
31.153	2.869	Weak	22.4
29.043	3.072	Weak	23.7
14.600	6.062	Weak	22.4
19.033	4.659	Weak	20.6

Form I is preferably ssentially free of Form II and/or other forms of Flavopiridol. "Essentially free" of Form II and/or other forms of Flavopiridol means

that Form II and/or other forms of Flavopiridol are present in l ss than 10%, 9%, 8%, 7%, 6%, 5%, 4% and 3% as shown by x-ray powder diffraction or Nucl ar Magnetic Resonance (NMR).

"Other forms of Flavopiridol" include base and salt forms as is appropriate, and which include hydrates, solvates or solvate hydrates, but does not include Form I or Form II.

"Form II" means the solvate/hydrate of ethanol/water of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride as described by x-ray powder diffraction in Table 2, obtained using Cu K-alpha radiation.

Table 2

2 Theta Angle (°)	D Space- Å	Relative Intensity (%)
6.920	12.763	100.0
13.850	6.389	35.7
27.908	3.194	22.2
6.669	13.244	18.0
20.838	4.259	13.8
7.339	12.036	13.8
31.660	2.824	9.5
10.208	8.659	8.3
14.722	6.012	7.2
16.413	5.397	6.9
25.829	3.447	6.5

Preferably, Form I is made by combining a sufficient quantity of Form II with a sufficient amount of an appropriate azeotropic solvent to form an azeotropic mixture; submitting the azeotropic mixture to azeotropic distillation sufficient to form Form I; and optionally recovering Form I.

A "sufficient quantity of Form II" is an amount to form crystals of Form I in the reaction mixture which can be recovered. One skilled in the art may xperimentally d termine this quantity.

A "sufficient quantity of a suitable solvent" is nough suitable solvent to at least partially dissolve Form II thus forming a reaction mixture and can be experimentally determined by one skilled in the art. The experiments described hereafter give examples of quantities that could be used.

"Appropriate conditions" in large part depend upon the suitable solvent selected. For example, if the appropriate conditions comprise azeoptropic distillation, an appropriate azeoptropic solvent will be selected.

A "suitable solvent" is a solvent that at least partially dissolves Form II, and permits the formation of crystals of Form I. The suitable solvent can be an "appropriate azeotropic solvent" or as otherwise described herein.

"Azeotropic mixture" refers to a liquid mixture of two or more substances which behaves like a single substance in that the vapor produced by partial evaporation of liquid has the same composition as the liquid. The constant boiling mixture exhibits either a maximum or minimum boiling point as compared with that of other mixtures of the same substance.

"Azeotropic distillation" refers to a type of distillation in which a substance is added to the mixture to be separated in order to form an azeotropic mixture with one or more of the constituents of the original mixture. Typically, the azeotropic mixture is heated to a temperature at which the solvate/water is driven off of Form II. The azeotropes thus formed will have boiling points different from the boiling points of the original mixture.

"Appropriate azeotropic solvent"(s), comprise ketone solvents such as acetone, methyl ethyl ketone and the like; aliphatic ester solvents such as ethyl acetate, methyl acetate, methyl formate, ethyl formate, isopropyl acetate and the like; mixtures of ketone solvents and aliphatic ester solvents; C_5-C_8 aliphatic solv nts such as pentane, h xane and the like; aliphatic nitril s, such as acetonitrile; benzene, toluene, pyridine, and so on. See for example Practical Organic Chemistry, 3rd ed., John Wiley &Sons, 1956 e.g., pp. 10-11, incorporated herein by reference.

As used herein, the term "suitable temp rature" refers to that temp rature which is permit the crystallization of Form I without substantial damage to the Form I thus formed. In the azeotropic distillation, it will be the boiling point at which the solvate and/or water has been driven off.

At this point, the Form I is in the form of a crystal which has precipitated and which may be recovered by isolating the crystal. Typically, this may be accomplished by filtering the crystal or evaporating the solvent or otherwise removing the solvent from the crystal, or the crystal from the solvent. Drying of the solvent, e.g. evaporation at ambient temperature or upon heating, may also be appropriate.

An important feature of Form I over Form II is the ability of Form I not to absorb water readily from the atmosphere. The present invention provides a form of Flavopiridol which has a weight gain due to water of less than 5%, including 4%, 3%, 2%, 1% and less than 1% in fractions (normally about 1-2%) with a Relative Humidity of about 75% and even up to a Relative Humidity of about 90% (weight gain of about 3.5%). Form II, as a solvate/hydrate, showed a slow but continual weight gain of about 4% through about 60% Relative Humidity. Above 60%, Form II showed a weight gain of about 15-20%.

EXAMPLE 1

Preparation of Flavopiridol Form I

Approximately 6 g of Flavopiridol Form II was placed in a 600 mL beaker. 300 mL of Methyl ethyl ketone (MEK) was added slowly, with stirring, to obtain a slurry. The solution was heated slowly to 50°C until cloudy. The temperature was increased to about 73°C with stirring and the addition of 100 ml of solvent. As the solution was brought to a strong boil it began to precipitate out and settle to the bottom. The temperature was increased and monitored to 80°C (boiling point of MEK), for a few minut s to obtain additional precipitate, then removed and allowed to cool to about 55°C. The final volume of 325 mL of solution required filtering through a Buchner funnel, under vacuum, using Whatman #1 filter paper, until dry; resulting in a dense yellow and flocculent chunk-like powder. The structure was confirmed by Mass

Sp ctrometry, Nuclear Magnetic Resonance and Fourier Transform Infra Red, and X-Ray powder diffraction performed on the sampl .

EXAMPLE 2

X-Ray Powder Diffraction Methodology

X-ray powder diffraction (XRPD) patterns were obtained on a Scintag XDS 2000 θ/θ diffractometer operating with copper radiation at 45kV and 40mA , using a Kevex Psi Peltier-cooled silicon detector. The source slits of 2 and 4 mm, and detector slits of 0.5 and 0.3 mm were used for data collection. Sample obtained was gently milled using an agate mortar and pestle for approximately one minute, placed in a platinum sample holder, and leveled using a glass microscope slide. Powder diffraction patterns of the samples were obtained from 2° to 42° 2θ at 1°/min. Calibration of the XDS 2000 is verified annually using a silicon powder standard.

EXAMPLE 3

Hygroscopicity screening - Comparison of Form I and Form II

Dynamic Vapor Sorption (DVS) analysis studies were conducted on Form II versus Form I.

Dynamic Water Vapor Sorption Analysis (DVS)

Form II was studied at 25°C using a Surface Measurement Systems Dynamic Vapor Sorption DVS-1 analyzer. A sample in the range of about 14.8 mg was placed in a tared quartz sample holder at an initial ambient room humidity setting of about 48% Relative Humidity (RH). A total wet/dry nitrogen flow rate of 200 cc/min was used throughout the study. The following full cycle program was initiated: 30 min at the initial ambient RH, followed by settings of 0, 20, 40, 60, 80, 90, 95 and 98%RH, with exposure time at each humidity set point dependent upon dm/dt being less than 0.001% for 60 min. The maximum time allowed at any one humidity set point was 24 hours. For a full cycle, data collection took about 4 days to complete. After the full cycle the sample was maintained at the same RH as the initial ambient starting RH.

Form I was studied at 25°C and 40°C using the DVS-1 analyzer. Data was collected over two full cycles. Samples of 10.4 and 16.7 mg were placed into respective tared quartz sample holders at an initial ambient room humidity setting of about 46%RH and 33%RH, resp ctively. For this study, an additional 75%RH s t point was used. For 2 full cycles, data collection took about 7 days at 25°C and

about17 days at 40°C to complete. After completion of ach 2 cycle study, the samples were maintained at the same RH as the initial ambi nt starting RH.

X-ray Powder Diffraction (XRPD) patterns were taken on a Scintag XDS 2000 θ/θ diffractometer operating with copper radiation at 45kV and 40 mA, using a Kevex Psi Peltier-cooled silicon detector. Source slits of 2 and 4 mm, and detector slits of 0.5 and 0.3 mm were used for data collection. Form II samples were gently milled using an agate mortar and pestle for approximately one minute, placed in a platinum sample pan, and leveled using a glass microscope slide. Samples taken during or post hygroscopicity testing were not milled due to the limited amount of sample available. In each case, powder diffraction patterns were scanned from 2° to 42° 2θ at 1°/minute. Calibration of the XDS 2000 was verified using Silicon powder.

For variable relative humidity experiments, the larger capacity DVS-2 Surface Measurement Systems Dynamic Vapor Sorption analyzer was used. Using a flow rate of 500cc/min, Form II was held at desired RH settings and sampled periodically for XRPD analysis. Unmilled material was placed in the platinum sample pan and leveled using a glass microscope slide prior to analysis using the above conditions.

Form II showed a slow but continual weight gain through about 60%RH of approximately 4%, and above 60% relative humidity an additional 15 - 20% weight gain was observed. In contrast, Form I showed an approximate weight gain of 1 - 2% through about 75%RH, plus an additional estimated 3.5% weight gain through about 90%RH. Above 90%RH, a weight gain of about 30% was observed. Thus, Form II would be considered hygroscopic, while Form I would be considered hygroscopic above 75%RH.

Variable humidity x-ray powder diffraction showed, that, as the humidity is increased there is an apparent decrease in crystallinity in Form II, and a significant change in the XRPD pattern which is presumably due to the loss of ethanol. Whereas Form I apparently retains its crystallinity until extremely high relative humidity is reached, (i.e., >98%) at which point it loses crystallinity and becomes amorphous.

Based upon these results, Form I has superior physical properti s for relative to Form II for use as a pharmaceutical composition.

EXAMPLE 4

Form II

A reactor is charged under nitrogen atmosphere with (-)-cis-1-methyl-4R-(2,4,6-trimethoxyphenyl)-3S-piperidinol) and acetic anhydride. Boron trifluoride etherate is added at a constant rate while stirring and cooling the resulting solution to 8-20°C. After the addition is complete the resulting mixture is stirred at 20-30°C for 3-5 hours. The reaction mixture is cooled to 8-12°C and ice-water is added while stirring followed by addition of aqueous sodium hydroxide until pH 10-11 is attained. The mixture is extracted with ethyl acetate. The ethyl acetate extracts are pooled and concentrated under vacuum. The residue is taken up in methanol and water. Then sodium hydroxide (about 50% aqueous solution) is added. The reaction mixture is stirred at 20-30°C for 2-3 hours. The mixture is evaporated under reduced pressure at $\leq$ 80°C. The residue is cooled to 15-20°C and brought to pH 8.5-9.5 using concentrated hydrochloric acid. A solid precipitates, which is collected by filtration washed with demineralized water and dried under reduced pressure to give ((-)-cis-1-methyl-4-(3-acetyl-4,6-dimethoxy-2-hydroxy)phenyl-3-piperidinol).

((-)-cis-1-methyl-4-(3-acetyl-4,6-dimethoxy-2-hydroxy)phenyl-3-piperidinol) is then added portionwise to a stirred suspension of potassium tert. butoxide in dry N,N-dimethylforamide at such a rate that the temperature does not exceed 20°C. After the addition is complete the resulting mixture is stirred for one hour at $\leq$30°C. Methyl 2-chlorobenzoate is added at such a rate, that the temperature does not exceed 30°C. the resulting mixture is stirred at 20-30°C for 4-6 hours. Demineralized water is added, followed by concentrated hydrochloric acid until the pH of the mixture reaches 6-8. The mixture is extracted two times using chloroform. The chloroform extracts are pooled together and concentrated under reduced pressure.

After cooling the remaining oil to $\leq$40°C, concentrated hydrochloric acid is added. The mixture is then stirred at $\leq$40°C for $\leq$ 2 hours or overnight is necessary. After cooling the reaction mixture to 15-30°C, water and chloroform are added. The

resulting mixture is basified to pH 8.5-10.5 using sodium hydroxide solution (50%). Th phas s are s parated. The aqueous layer is then extracted with chloroform. The combined organic extracts are evaporated under reduced pressure to yield (-)-cis-2-(2-Chlorophenyl)-5,7-dimethoxy-8-[4R-(3S-hydroxy-1-methyl)-piperidinyl]-4H-1-benzopyran-4-one as an oil, which is directly used in the next step without purification.

To (-)-cis-2-(2-Chlorophenyl)-5,7-dimethoxy-8-[4R-(3S-hydroxy-1-methyl)-piperidinyl]-4H-1-benzopyran-4-one, quinoline and pyridine hydrochloride are added. The resulting mixture is heated to 160-190°C while stirring. Stirring is continued while maintaining the temperature at 160-190°C for 2 hours. After cooling the reaction mixture to 90-110°C water is added. The resulting mixture is basified to pH 7.5-8.5 using saturated sodium carbonate solution. A mixture of ethanol twice with a mixture of ethanol and chloroform. The combined extracts are evaporated to dryness to obtain (+)-cis-2-(2-chloropheny)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one crude as a brown gum, which is purified as follows.

To (+)-cis-2-(2-chloropheny)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one crude, acetone is added. The resulting mixture is stirred at 55-60°C for 30-60 minute, then cooled to 15-20°C and stirred for another 1-2 hours. The precipitated solid is isolated by filtration, washed twice with acetone and dried under reduced pressure to give (+)-cis-2-(2-chloropheny)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one in a purified form.

The free base from the previous step is suspended in ethanol and acidified using concentrated hydrochloric acid at such a rate that the temperature does not exceed 30°C. During this process initially all of the solid dissolves and then the hydrochloride precipitates. The suspension is cooled to 0-10°C and stirred for 1 hour while maintaining the temperature. The crystals are isolated by filtration and washed with cold ethanol to yield (-)-cis-2-(2-chloropheyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4-H-1-benzopyran-4-one hydrochloride, crude.

To (-)-cis-2-(2-chloroph yl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4-H-1-benzopyran-4-one hydrochloride, crude, ethanol is added. The resulting mixture is heated to 70-79°C, stirred for 1 hour while maintaining the temperature and then filtered while still hot. The filter is rinsed with hot ethanol. The filtrate is concentrated by atmospheric distillation, until 60-80% of the volatives have been removed. The remaining suspension is then cooled to 0-10°C while isolated by filtration and dried under reduced pressure to give (-)-cis-2-(2-chloropheyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4-H-1-benzopyran-4-one hydrochloride, purified as a yellow solid.

After the Form I is recovered, a pharmaceutical composition can be prepared. As used herein, "pharmaceutical composition" means a therapeutically effective amount of Form I with a pharmaceutically acceptable carrier.

A "pharmaceutically acceptable carrier" is an agent which is non-toxic, does not interfere with the therapeutic profile of Form I and is appropriate to the method of administration. Form I is preferably administered by the intravenous route over an appropriate period of time for cancer chemotherapy. Preferably, Form I is mixed with one or more pharmaceutically acceptable carriers. For example, Form I may be mixed with iso-ismotic and pH controlled liquids such as water, dextrose/water or saline/water for injection intravenously into the patient.

An "effective amount" includes a "therapeutically effective amount", "an effective protein kinase inhibiting amount", "an effective cyclin dependent kinase amount" and an effective tumor-inhibiting amount of Form I and will vary with the individual, concomitant therapy, the disease, and other variable factors. An effective amount for Form I will be about the same as for Form II. Typically, the dosage of Form I will be 0.001mg/kg to 100 mg/kg per day.

Flavopiridol is us ful in treating a number of conditions or diseases that benefit from inhibition of protein kinases, and more particularly cyclin dep ndent kinases as pr viously described herein. Flavopiridol is xpected to be useful in treating a broad

range of cancers including, for exampl , l ukemia, mesothelioma and cancers of the lung (large cell, small, cell and non-small cell), colorectal, breast, ovarian, prostate melanoma, renal, uterine body and central nervous system.

All articles and patents cited herein are hereby incorporated herein by reference.

What is claimed is:

1. Pseudopolymorph Form I having an x-ray powder diffraction pattern expressed in terms of "D" spacing:

D space- Å
12.708
4.323
5.594
5.349
3.590.

2. A pseudopolymorph Form I having an x-ray powder diffraction pattern expressed in terms of "D" spacing and relative intensities thereof:

D space- Å	Relative Intensity
12.708	Strong
4.323	Strong
5.594	Strong
5.349	Medium
3.590	Medium
3.366	Medium
4.209	Medium
3.395	Medium
3.438	Medium
4.839	Medium.

3. A pseudopolymorph Form I having an x-ray powder diffraction pattern expressed in terms of "D" spacing and percentage of relative intensities thereof:

D space- Å	Relative Intensity %
12.708	100.0
4.323	75.9
5.594	58.5
5.349	49.5
3.590	46.6
3.366	42.0
4.209	40.7
3.395	39.5
3.438	38.8
4.839	37.1.

4. A pseudopolymorph Form I having an x-ray powder diffraction pattern as d fin d in Tabl 1:

Table 1

2 Theta Angle (°)	D Space - Å	Relative Intensity	Relative Intensity (%)
6.950	12.708	Strong	100.0
20.529	4.323	Strong	75.9
15.830	5.594	Strong	58.5
16.560	5.349	Medium	49.5
24.778	3.590	Medium	46.6
26.457	3.366	Medium	42.0
21.091	4.209	Medium	40.7
26.226	3.395	Medium	39.5
25.898	3.438	Medium	38.8
18.320	4.839	Medium	37.1
8.308	10.634	Medium	35.7
23.748	3.744	Medium	33.4
13.010	6.799	Medium	32.4
30.520	2.927	Medium	31.0
27.106	3.287	Weak	26.2
31.153	2.869	Weak	22.4
29.043	3.072	Weak	23.7
14.600	6.062	Weak	22.4
19.033	4.659	Weak	20.6.

5. The Form I of claims 1, 2, 3 or 4 wherein the Form I is essentially free of Form II.

6. The Form I of claims 1, 2, 3 or 4 wherein the Form I is essentially free of Form II and other Forms of Flavopiridol.

7. The Form I of claims 1, 2,3 or 4 wherein Form II and other forms of Flavopiridol are present in less than 4%.

8. A pharmaceutical composition comprising a therapeutically effective amount of Form I of claim 1,2,3 or 4 and a pharmaceutical acceptable carrier.

9. A pharmaceutical composition comprising a therapeutically effective amount of the Form I of claim 1,2,3 or 4, which is ssentially free of Form II, and a pharmaceutical acceptable carrier.

10. A pharmaceutical composition comprising a therapeutically effective amount of the Form I of claim 1,2,3 or 4, which is essentially free of Form II and other forms of Flavopiridol, and a pharmaceutical acceptable carrier.

11. A method of treating a patient for cancer by administering to the patient a therapeutically effective amount of Form I of claim 1, 2, 3 or 4.

12. The method of claim 11 wherein the Form I is essentially free from Form II or other Flavopiridol forms.

13. A method of inhibiting protein kinases in a patient by administering to the patient in need thereof an effective protein kinase inhibiting amount of the Form 1 of claims 1, 2, 3 or 4.

14. The method of claim 13 wherein the Form I is essentially free from Form II or other forms of Flavopiridol.

15. A method of inhibiting cyclin dependent kinases in a patient by administering to the patient in need thereof an effective cyclin dependent kinase inhibiting amount of Form I of claims 1, 2, 3 or 4.

16. The method of claim 15 wherein the Form I is essentially free from Form II or other forms of Flavopiridol.

17. A method of making the Form I of claims 1, 2,3 or 4 comprising

(a) combining a sufficient quantity of Form II with a sufficient amount of an apropriate azeotropic solvent, thus forming an azeotropic mixture;

(b) submitting the az otropic mixture to azeotropic distillation sufficient to form Form 1; and

(c) optionally recovering Form I therefrom.

18. The method of claim 17 wherein th solvent is a ketone solv nt.

19. The method of claim 17 wherein the solvent is methyl ethyl ketone.

20. The method of claim 15 wherein the crystallized Form I is recovered by filtering Form I.

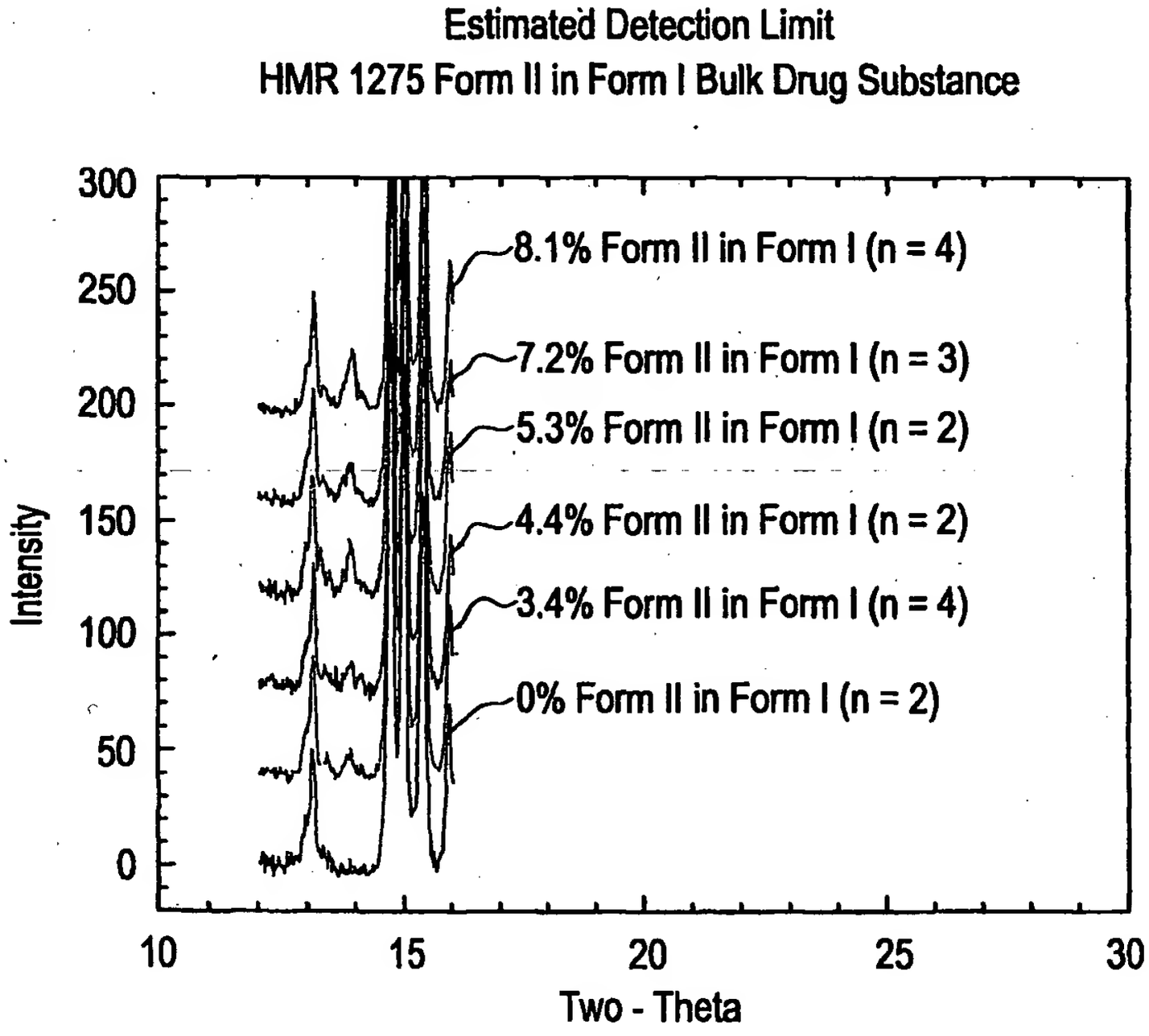
21. The method of claim 15 wherein the temperature of the azeotropic distillation is about 73 °C to about 80 ° C.

22. A form of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one or one of its pharmaceutically acceptable salts characterized by a weight gain due to water of less than five percent at a relative humidity of about 75%.

23. A form of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride characterized by a weight gain due to water of less than five percent at a relative humidity of about 75%.

24. The Form I of claims 1, 2,3 or 4 for use as a pharmaceutically active compound.

FIG. 1


Estimated Detection Limit
HMR 1275 Form II in Form I Bulk Drug Substance
Intensity
300
250
200
150
100
50
0
10
15
20
25
30
Two - Theta
8.1% Form II in Form I (n = 4)
7.2% Form II in Form I (n = 3)
5.3% Form II in Form I (n = 2)
4.4% Form II in Form I (n = 2)
3.4% Form II in Form I (n = 4)
0% Form II in Form I (n = 2)

INTERNATIONAL SEARCH REPORT

ernational Application No
PCT/US 01/00519

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D405/04 A61K31/435 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 284 856 A (NAIK RAMCHANDRA G ET AL) 8 February 1994 (1994-02-08) cited in the application column 8, line 51; example 9	1-24
X	LI, PING ET AL: "Evaluation of intravenous flavopiridol formulations" PDA J. PHARM. SCI. TECHNOL. (1999), 53(3), 137-140 , XP000995938 figures 1,2	1-24
A	SEDLACEK ET AL.: "Flavopiridol, a new kinase inhibitor for tumor therapy" INT. J. ONCOLOGY, vol. 9, pages 1143-1168, XP002103774 cited in the application the whole document	1-24

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 May 2001	11/05/2001

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/00519

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